

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

A. NADA Number: 141-070

B. Sponsor: Schering-Plough Animal Health Corporation
1095 Morris Avenue
Union, N. J. 07083

C. Generic Name: Propofol

D. Trade Name: RAPINOVET

E. Marketing Status: Rx

F. Effect of Supplement:

1. The supplement supports the addition of a new species, cats, to the original approved dog application for the same anesthetic indications.

2. The supplement also contains changes to the original canine portions of the label and FOI Summary as follows:

a. Information concerning the use of medetomidine prior to propofol anesthesia in dogs will appear on the label as well as in the FOI Summary. Medetomidine is approved for use in dogs for sedation and analgesia.

b. The recommended preanesthetic medetomidine dose will be lowered from 10-40 ug/kg IM/IV to 5-10 ug/kg IM based on data already contained in the original new animal drug application (NADA) approval for propofol in dogs.

NOTE: This FOI Summary contains all the original information that was provided in the FOI Summary for dogs as well as the supplemental canine label/FOI changes and complete information for the supplemental approval for propofol's use in cats. Therefore, this FOI Summary supercedes the original 1996 FOI Summary for NADA 141-070.

2. INDICATIONS FOR USE:

RAPINOVET is an anesthetic injection approved for use in dogs and cats as follows:

- a. As a single injection to provide general anesthesia for short procedures.
- b. For induction and maintenance of general anesthesia using incremental doses to effect.
- c. For induction of general anesthesia where maintenance is provided by inhalant anesthetics.

Propofol is an effective anesthetic when used in accordance with good veterinary anesthetic practices. Propofol properties include smooth induction and rapid recovery. Propofol may be used alone to induce a relatively short period of anesthesia. Propofol may also maintain anesthesia for longer periods, through intermittent injections. Both induction and maintenance may be preceded by a pre-anesthetic drug(s). Finally, propofol may be used to induce anesthesia that will be maintained with an inhalant anesthetic.

Induction of anesthesia will usually be observed within 30-60 seconds after the end of administration (administration should take 60-90 seconds). The duration of anesthesia following the recommended induction dose (5.5 - 7.0 mg/kg for dogs without premedication or 8.0-13.2 mg/kg for cats without premedication) is generally 5 - 7 minutes for dogs and 5-12 minutes for cats. The duration of anesthesia following maintenance doses varies depending upon the dose; for dogs, it is generally 2 - 6 minutes after 1.1 mg/kg and 6 - 10 minutes after 3.3 mg/kg; for cats, it is generally 5-7 minutes after 1.1 mg/kg and 12-18 minutes after 4.4 mg/kg. RAPINOVET is particularly suitable for cases where a rapid recovery is required. Full standing recovery is generally observed within 10-20 minutes for dogs and within 30-45 minutes for cats after the end of anesthesia, regardless of the duration of anesthesia. Recovery may be delayed in sighthounds or if pre-anesthetics are administered.

3. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGES:

RAPINOVET is an oil in water emulsion containing 10 mg of propofol per mL. It is available in a 20 mL sealed ampule, and is intended for intravenous use only.

A. INDUCTION OF GENERAL ANESTHESIA:

For induction, RAPINOVET injection should be titrated against the response of the patient over approximately 60 - 90 seconds or until clinical signs show the onset of anesthesia. The average induction dose ranges and dosage rates for healthy dogs and cats given propofol alone, or when propofol is preceded by premedicants, are indicated in the following tables (the tables are for guidance only; in practice, the dose should be based upon patient response):

Induction Dosage Guidelines for DOGS:

Preanesthetic	Propofol Induction Dose		Propofol Rate of Administration		
	mg/kg	mg/lb	seconds	mg/kg/min	mL/kg/min
None	5.5-7.0	2.5-3.2	60-90	3.7-7.0	0.37-0.70
Acepromazine	4.0-4.4	1.8-2.0	60-90	2.7-4.4	0.27-0.44
Xylazine	2.2-3.3	1.0-1.5	60-90	1.5-3.3	0.15-0.33
Oxymorphone	2.2-3.3	1.0-1.5	60-90	1.5-3.3	0.15-0.33
Medetomidine	2.2-2.8	1.0-1.3	60-90	1.5-2.8	0.15-0.28
Butorphanol	4.4-5.0	2.0-2.3	60-90	2.9-5.0	0.29-0.50
Acepromazine/ Butorphanol	2.2-2.8	1.0-1.3	60-90	1.5-2.8	0.15-0.28

The recommended dosages of tranquilizers, sedatives, or analgesics administered as preanesthetic medications (listed below) may be lower than the label directions for use as a single medication (see references: Thurmon et al., 1996, Mallinckrodt/Schering-Plough Animal Health clinical studies).

Acepromazine	0.03 - 0.1 mg/kg	IM, SC, IV
Xylazine	0.25 - 0.5 mg/kg	IV
	0.5 - 1.0 mg/kg	IM, SC
Oxymorphone	0.1 - 0.2 mg/kg	IM, SC, IV
Medetomidine	5-10 µg/kg	IM
Butorphanol*	0.1 - 0.3 mg/kg	IM, SQ

*The safety of general anesthesia with propofol when used in conjunction with butorphanol was evaluated. However, butorphanol is not approved as a preanesthetic in dogs.

The preanesthetic use of the drugs listed above markedly reduces propofol requirements. As with other sedative hypnotic agents, the amount of phenothiazine, opioid, and/or alpha-2 agonist premedication will influence the response of the patient to an induction dose of RAPINOVET. The

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induction dose will also be influenced by the interval between the administration of premedication and induction and the rate of administration of propofol.

If RAPINOVET is injected too slowly (> 90 seconds), an inadequate plane of anesthesia may result. If this occurs, an additional low dose of propofol may be administered (1.1 mg/kg) to facilitate intubation or the transition to inhalant maintenance anesthesia.

Propofol Induction Dosage Guidelines for CATS:

Preanesthetic	Propofol Dose		Propofol Rate of Administration		
	mg/kg	mg/lb	seconds	mg/kg/min	mL/kg/min
None	8.0 - 13.2	3.6 - 6.0	60 - 90	5.3 - 13.2	0.53 - 1.32
Acepromazine	8.0 - 13.2	3.6 - 6.0	60 - 90	5.3 - 13.2	0.53 - 1.32
Butorphanol	8.0 - 13.2	3.6 - 6.0	60 - 90	5.3 - 13.2	0.53 - 1.32
Oxymorphone	8.0 - 13.2	3.6 - 6.0	60 - 90	5.3 - 13.2	0.53 - 1.32
Xylazine	7.0 - 12.0	3.2 - 5.5	60 - 90	4.7 - 12.0	0.47 - 1.20
Acepromazine / Butorphanol	7.7 - 9.9	3.2 - 5.5	60 - 90	5.1 - 9.9	0.51 - 0.99
Acepromazine / Oxymorphone	8.0 - 12.0	3.6 - 5.5	60 - 90	5.3 - 12.0	0.53 - 1.20

The recommended dosages of tranquilizers, sedatives, or analgesics administered as preanesthetic medications may be lower than the label directions for use as a single medication (see references: Thurman et al., 1996; Peterson, 1997; Sawyer and Campbell, 1997; Plumb, 1995; Branson, et al.).

Acepromazine	0.03 - 0.1	IM, IV, SC
Butorphanol	0.1 - 0.3	IM, SC
Oxymorphone	0.05 - 0.2	IM, IV
Xylazine	0.25 - 0.5	IV
	0.4 - 1.0	IM, SC

The preanesthetic use of the drugs listed above may reduce propofol requirements. As with other sedative hypnotic agents, the amount of phenothiazine, opioid, and/or α -2 agonist premedication will influence the response of the patient to an induction dose of RAPINOVET. The induction dose will also be influenced by the interval between the administration of premedication and induction, and by the rate of administration of propofol.

If RAPINOVET is injected too slowly (> 90 seconds), an inadequate plane of anesthesia can occur. If this happens, an additional low dose of propofol (1.1 mg/kg) may be administered to facilitate intubation or the transition to inhalant maintenance anesthesia.

B. MAINTENANCE OF GENERAL ANESTHESIA:

1) Intermittent Propofol Injections:

Anesthesia can be maintained by administering propofol in intermittent IV injections. Clinical response will be determined by the amount, the rate of administration, and the frequency of maintenance injections. The following tables are provided for guidance:

Maintenance Dose Guidelines for DOGS:

Preanesthetic	Propofol Maintenance Dose		Propofol Rate of Administration		
	mg/kg	mg/lb	seconds	mg/kg/min	mL/kg/min
None	1.1-3.3	0.5-1.5	30-60	1.1-3.3	0.11-0.33
Acepromazine	1.1	0.5	30-60	1.1-2.2	0.11-0.22
Xylazine	1.1	0.5	30-60	1.1-2.2	0.11-0.22
Oxymorphone	1.1	0.5	30-60	1.1-2.2	0.11-0.22
Medetomidine	1.1	0.5	30-60	1.1-2.2	0.11-0.22
Butorphanol	1.5	0.7	30-60	1.5-3.0	0.15-0.30
Acepromazine/ Butorphanol	1.1	0.5	30-60	1.1-2.2	0.11-0.22

Repeated maintenance doses of propofol do not result in increased recovery times, indicating that the anesthetic effects of propofol are not cumulative in dogs.

Maintenance Dosage Guidelines for CATS:

Preanesthetic	Propofol Dose		Propofol Rate of Administration		
	mg/kg	mg/lb	seconds	mg/kg/min	mL/kg/min
None	1.1 - 4.4	0.5 - 2.0	30 - 60	1.1 - 4.4	0.11 - 0.44
Acepromazine	1.1 - 4.4	0.5 - 2.0	30 - 60	1.1 - 4.4	0.11 - 0.44
Butorphanol	1.1 - 4.4	0.5 - 2.0	30 - 60	1.1 - 4.4	0.11 - 0.44
Oxymorphone	1.1 - 4.4	0.5 - 2.0	30 - 60	1.1 - 4.4	0.11 - 0.44
Xylazine	1.1 - 2.2	0.5 - 1.0	30 - 60	1.1 - 2.2	0.11 - 0.22
Acepromazine / Butorphanol	1.1 - 3.3	0.5 - 1.5	30 - 60	1.1 - 3.3	0.11 - 0.33
Acepromazine / Oxymorphone	1.1 - 3.3	0.5 - 1.5	30 - 60	1.1 - 3.3	0.11 - 0.33

Administering repeated maintenance doses of propofol results in slightly increased recovery times, indicating that the anesthetic effects of propofol may be cumulative in the cat.

2) Maintenance by Inhalant Anesthetics:

Clinical trials using propofol have shown that it may be necessary to use a higher initial concentration of the inhalant anesthetic than is usually required following induction using barbiturate anesthetics, due to rapid recovery from RAPINOVET.

4. EFFECTIVENESS:

I. THE EFFICACY OF PROPOFOL IN DOGS WAS DEMONSTRATED IN THREE PIVOTAL STUDIES:

A. DOSE DETERMINATION STUDY:

Phase 1: Propofol Alone for Induction of Anesthesia

Phase 2: Propofol Alone for Maintenance of Anesthesia

B. COMPATIBILITY OF PROPOFOL IN DOGS WHEN USED WITH
PREANESTHETICS AND INHALANT ANESTHETICS

C. CLINICAL TRIAL UNDER FIELD CONDITIONS WITH PROPOFOL IN DOGS

A. DOSE DETERMINATION STUDY: INDUCTION PHASE 1:

Investigator:

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Sponsor Monitors:

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The objective of the study was to determine an effective induction dose and the mean duration of anesthesia in dogs. The formulation for the injectable anesthetic was the same as the market formulation. Placebo controls were not used due to the nature of the drug being investigated (anesthetic). Each dog served as its own control in that it was either anesthetized or not anesthetized as determined by reflex response to tail clamp, purposeful movements, or other clinical observations.

Short and Salsbury (1994a) conducted the induction dose determination study in 30 mongrel dogs. The dogs were divided into 3 groups of 5 males and 5 females each. Propofol was administered as a single intravenous dose of 3.3, 6.6, or 9.9 mg/kg delivered during periods of approximately 25, 60, or 90 seconds, respectively (dose rate approximately 6.6 mg/kg/min). Observations included induction time, duration of anesthesia, recovery time, respiratory rate, pulse rate, mean arterial blood pressure, oxygen saturation, and adverse reactions. Most dogs received routine supplemental oxygen when oxygen saturation levels decreased below 90%.

RESULTS:

Duration of anesthesia:

The following table lists the individual values for duration of anesthesia for each dose group:

Duration of Anesthesia vs. Dose:

3.3 mg/kg	6.6 mg/kg	9.9 mg/kg
range 0-3.01 min	range 2.35-11.02 min	range 5.53-23.46 min
0 min	7.05 min	12.39 min
0	6.58	10.59
3.01	10.03	15.55
0	9.54	5.53
0	4.01	14.05
0	3.12	10.02
0	11.02	16.14
2.03	2.35	12.11
1.03	5.24	9.00
0	5.04	23.46

The 3.3 mg/kg dose failed to induce anesthesia in some dogs (7 of 10). The dose of 6.6 mg/kg demonstrated adequate periods of anesthesia without apnea. The mean duration of anesthesia was 6 minutes and 32 seconds (6:32; range 2:35 - 11:02).

Duration of anesthesia was significantly longer ($p < 0.05$) in the 9.9 mg/kg dose group than in the 6.6 mg/kg dose group by Kruskal-Wallis test. However, despite oxygen supplementation (administered when oxygen saturation decreased below 90%), four dogs experienced apnea among the 10 dogs in the 9.9 mg/kg dose group compared to none in the 6.6 mg/kg dose group. This difference was statistically

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significant by the Fisher's Exact test ($p < 0.05$). Based upon these results, the 9.9 mg/kg dose produced excessive anesthesia as judged by the occurrence of apnea in four dogs (severe in three dogs).

Recovery Time:

The following table lists individual recovery times in minutes (beginning of anesthesia until standing recovery) for each dose group:

Recovery Time vs. Dose:

3.3 mg/kg	6.6 mg/kg	9.9 mg/kg

range 7.08-20.56 min	range 12.20-28.06	range 16.41-83.41

7.08 min	22.33 min	18.59 min
12.32	22.25	25.38
7.59	22.31	29.04
20.56	21.33	23.55
13.	21.01	27.47
7.29	13.57	19.19
17.14	28.06	19.44
7.16	17.59	22.01
18.22	21.51	16.41
18.26	12.20	83.41

In the 6.6 mg/kg group, the mean time from end of anesthesia to full standing recovery was 13:54 minutes:seconds (range 7:16 - 17:00). One dog in the 9.9 mg/kg dose group experienced an excessively long recovery period.

Heart Rate (HR):

There was a tendency for HR to increase immediately after induction (increase in rate with normal sinus rhythm). No cardiac arrhythmias were observed.

Respiratory Rate (RR):

Respiration rates generally decreased following administration of propofol, especially at two minutes post-induction. There was conclusive evidence of respiratory depression ($RR < 8$ breaths/minute) in the 9.9 mg/kg dose group. Four dogs in this group experienced apnea, three of which were severe (> 5 minutes). Respiratory depression was also seen in the 6.6 mg/kg dose group but was of short duration.

Oxygen Saturation:

Oxygen supplementation was administered when oxygen saturation decreased below 90%. In the 6.6 mg/kg group, values returned to normal when the animals were given supplemental oxygen. No adverse reactions were noted in the 6.6 mg/kg group. Three dogs in the 9.9 mg/kg dose group required assisted ventilation as well as supplemental oxygen.

Blood Pressure (BP):

BP measurements were within physiologically acceptable ranges and were adequately maintained during anesthesia.

Conclusion:

Based upon these results, the recommended dose of propofol for induction of anesthesia is 6.6 mg/kg, delivered at an even rate over 60 - 90 seconds.

A. DOSE DETERMINATION STUDY: MAINTENANCE PHASE 2:

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Short and Salsbury (1994b) conducted a maintenance dose titration study in 30 mongrel dogs. The dogs were divided into 3 groups of 5 males and 5 females each. Propofol was administered to all dogs as a single induction dose at 6.6 mg/kg, delivered during a period of approximately 60 seconds. When each animal started to recover from anesthesia (by reacting to tail clamping, purposeful movements or other

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clinical signs), a maintenance dose of propofol was administered. This procedure was repeated as necessary until the dog had been anesthetized for a total of 30 minutes. Doses selected were 1.1, 3.3, and 5.5 mg/kg, given during 30, 60, or 90 seconds, respectively. Observations included induction time, duration of anesthesia, and recovery time; number of doses and dose volume; respiratory rate; pulse rate; mean arterial blood pressure; oxygen saturation; and adverse reactions. All dogs received supplemental oxygen during the study at least once (when oxygen saturation < 90%). The observers in the Phase 2 Maintenance Dose study were not blinded to the maintenance dose that was administered since parameters could be measured objectively or evaluated as "yes" or "no", and the animals served as their own controls.

RESULTS:

Anesthesia:

In the 1.1 mg/kg maintenance dose group, the average number of maintenance doses required for 30 minutes anesthesia was 9.9 (range 7 - 15), and the average time from the end of anesthesia to full standing recovery was 16 min:50 sec (range 8:17 - 27:37).

An average of 3.6 doses was required (range 3 - 5) for 30 minutes of anesthesia in the 3.3 mg/kg dose group, and the average time from the end of anesthesia to full standing recovery was 15:17 (range 7:05 - 25:44).

Recovery times did not differ between the 1.1 and 3.3 mg/kg dose groups.

Apnea:

The following table shows the occurrence of apnea during induction (6.6 mg/kg) and during maintenance for each of the maintenance dose groups:

Maintenance Dose	Apnea (induction) Group Dose = 6.6 mg/kg	Apnea during Maintenance
1.1 mg/kg	3	1
3.3 mg/kg	0	3
5.5 mg/kg	3	8*

* four dogs required IPPV

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Six of 30 dogs experienced apnea during induction (6.6 mg/kg). Four dogs experienced apnea in either the 1.1 mg/kg maintenance group (1 dog) or in the 3.3 mg/kg group (3 dogs). Eight of 10 dogs experienced apnea in the 5.5 mg/kg maintenance group.

The 5.5 mg/kg supplemental dose produced excessive respiratory depression as judged by apnea in 8 of 10 dogs. Four of the 8 dogs required intermittent positive pressure ventilation (IPPV). Apnea precluded the administration of another maintenance dose of 5.5 mg/kg at the first sign of incomplete anesthesia in these 8 dogs. The number of occurrences of apnea in this group was statistically significantly more than in the two lower maintenance dose groups.

Heart Rate and Blood Pressure:

Physiological responses were similar to those observed during the induction dose titration study (within acceptable ranges).

Side Effects:

Apnea is the most common side effect associated with the administration of propofol. All dogs received and responded to the receipt of supplemental oxygen.

Other side effects noted during the study included inadequate muscle relaxation (one during induction and one during recovery) and opisthotonos during recovery (two). Measurement of all parameters could not be accomplished in two dogs in the 1.1 mg/kg dose group due to insufficient duration of anesthesia.

Conclusion:

Based on these results, anesthesia can be maintained with propofol in the range of 1.1 - 3.3 mg/kg, delivered at an even rate over a period of approximately 30 - 60 seconds (depending on dose). The duration of anesthesia can be regulated by selection of the dose (lower doses for shorter duration; higher doses for longer duration).

B. COMPATIBILITY OF PROPOFOL IN DOGS WHEN USED WITH PREANESTHETICS
AND INHALANT ANESTHETICS

Study Director:

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Study Dates: May, 1993-July, 1994

Sponsor Monitors:

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Short and Campbell (1995) conducted a sequential series of drug trials on the compatibility of propofol when used in combination with various pre-anesthetics for induction of anesthesia.

Objective: To determine the pharmacophysiological responses to propofol when used in conjunction with various preanesthetics and when used as an induction agent to inhalational anesthetics.

Study Design: Thirty-six mongrel dogs (18 males and 18 females) approximately one year old and 33-65 pounds were used in the study. The same dogs had been previously used in the dose determination studies (P210-007 and P210-008). Each dog was used approximately three times (range 1-5 times) during the study.

Each of 17 groups contained 6 dogs. One group each was premedicated with atropine, glycopyrrolate, acepromazine, diazepam, oxymorphone, xylazine, and butorphanol; medetomidine was administered at two levels. One group received both acepromazine and butorphanol prior to propofol (Note: The safety of general anesthesia with propofol when used in conjunction with butorphanol was evaluated. However, butorphanol is not approved as a preanesthetic in dogs).

The dose for propofol was reduced in most groups depending on the sedative effect of the premedicant. The reduction in induction dose of propofol was selected based upon knowledge of drug mechanisms of action or experience with the pre-anesthetic drug(s) in combination with other anesthetics. Induction and recovery times were compared to results from Phase I (induction using propofol only) of the dose determination study.

Three groups received propofol as an induction agent and were maintained for 30 minutes using halothane, isoflurane, or methoxyflurane. Three other groups were pretreated with atropine, atropine plus acepromazine, or atropine plus medetomidine, then induced and maintained with propofol for 30 minutes. Induction and recovery times were compared to results from Phase II (propofol maintenance) of the dose determination study. The compatibility study was not blinded.

Observations included induction time, duration of anesthesia, recovery time, pulse (HR), respiration rate (RR), systolic, diastolic, and mean arterial blood pressure (BP), oxygen saturation, electroencephalograms (EEG for propofol and inhalant maintenance groups only), and adverse reactions.

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Propofol was administered slowly IV over 15 to 65 seconds, depending on the dose. For example, a dose of 2.2 mg/kg was given over 20 seconds; a dose of 6.6 mg/kg was administered over 60 seconds.

Treatment Groups:

Group	Drug	Dose	Group	Drug	Dose

1	propofol atropine	6.6 mg/kg IV 0.04 mg/kg IM	9	propofol isoflurane oxygen	6.6 mg/kg IV 0.6-2.5% * 2 L/min
2	propofol glycopyr	6.6 mg/kg IV 0.01 mg/kg IM	10	propofol	6.6 mg/kg IV
3	propofol acepromaz	4.4 mg/kg IV 0.1 mg/kg IM		methoxyfl oxygen	0.1-0.5% * 2 L/min
4	propofol diazepam	4.4 mg/kg IV 0.2 mg/kg IV	11	propofol halothane oxygen	6.6 mg/kg IV 0.5-1.8% * 2 L/min
5	propofol oxymorph propofol	3.3 mg/kg IV 0.1 mg/kg IV 1.1 mg/kg IV@	12	atropine propofol	0.02 mg/kg IM 6.6 mg/kg IV#
6	propofol medetom atropine	3.3 mg/kg IV 5 µkg IM 0.02 mg/kg IM	13	atropine acepromaz propofol propofol	0.02 mg/kg IM 0.1 mg/kg IM 4.4 mg/kg IV# 1.1 mg/kg IV@
7	propofol medetom atropine	2.2 mg/kg IV 10 µkg IM 0.02 mg/kg IM	14	atropine	0.02 mg/kg IM
7.2^	propofol medetom atropine atipamezole	2.2 mg/kg IV 10 µkg IM 0.2 mg/kg IM 30 µkg IV	15	medetom propofol propofol	10 µkg IM 2.2 mg/kg IV# 1.1 mg/kg IV@
8	propofol xylazine	2.2 mg/kg IV 0.5 mg/kg IM	16	butorphan propofol	0.2 mg/kg IM 4.4 mg/kg IV
* or as the inhalant anesthetic was required (to effect)				acepromaz butorphan	0.1 mg/kg IM 0.2 mg/kg IM

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^a group 7 was repeated using atipamezole for medetomidine reversal

Results:

All dogs in all groups were adequately anesthetized with propofol, with one exception (one was refractive to acepromazine). Medetomidine premedicated dogs received low induction doses of propofol (2.2 mg/kg) and frequently required another low dose of propofol (1.1 mg/kg) to be successfully intubated. No dogs in any groups died, and no uncontrollable adverse reactions were observed.

Duration of anesthesia is the time elapsed from the beginning of anesthesia and does not include premedicant or induction times. Recovery times were calculated by subtracting "walk" time (standing recovery) from "sleep" (anesthesia) times.

The following results are grouped according to type of premedicant (anticholinergic, tranquilizer, etc.); therefore, the group numbers are not in order. Conclusions were drawn from inspection of the means of the observed variables for each group. In general, physiological effects were dependent on the premedicant that was administered.

Anticholinergics:

Either atropine (group 1) or glycopyrrolate (group 2) were given 15 minutes before propofol induction. Propofol was given at 6.6 mg/kg over 60 seconds. All dogs were anesthetized.

The following table shows average values in minutes for the duration of anesthesia and recovery times for groups 1 and 2 compared to results from Phase I of the dose determination study.

Group	Duration of Anesthesia	Recovery Time
Phase I (propofol only)	6.53 min	13.90 min
Group 1	8.26 min	13.95 min
Group 2	8.47 min	11.65 min

Duration of anesthesia and recovery times were not different between groups 1 and 2, and were similar to the duration and recovery times observed during Phase I (induction only) of the dose determination study.

Physiological responses were unremarkable except for an expected increase in heart rate (HR). Increases in HR were greater using atropine; no arrhythmias were noted on the ECG monitor and no adverse effects observed.

Apnea occurred in one atropine treated dog and all dogs developed respiratory depression observed as a reduction in oxygen saturation below 90%. These side effects are due to propofol and not to the anticholinergics and all dogs responded to oxygen administration.

Tranquilizers (acepromazine, diazepam) or Sedatives (xylazine, alpha-2-agonist):

Three groups of six dogs each were premedicated as follows:

- Group 3 (acepromazine): propofol dose reduced to 4.4 mg/kg
- Group 4 (diazepam): propofol dose reduced to 4.4 mg/kg
- Group 8 (xylazine): propofol dose reduced to 2.2 mg/kg

The following table shows average values in minutes for the duration of anesthesia and recovery times for groups 3, 4, and 8 compared to results from Phase I of the dose determination study.

Group	Duration of Anesthesia	Recovery Time
Phase I (propofol only)	6.53 min	13.90
3 (acepromazine)	9.23	25.83
4 (diazepam)	5.94	13.87
8 (xylazine)	11.31	32.91

Premedication with diazepam coupled with a reduced propofol induction dose (4.4 mg/kg, 33% reduction in propofol dose) resulted in anesthesia and recovery times similar to groups that did not receive tranquilizing agents (as in groups 1 and 2).

Premedication with acepromazine was not associated with a prolongation of anesthesia time at the reduced propofol dose (4.4 mg/kg, 33% reduction in propofol dose); however, recovery time was slower.

Duration of anesthesia and recovery times were both lengthened following premedication with xylazine (propofol dose = 2.2 mg/kg, 67% reduction in propofol dose).

Sedative-medetomidine (alpha-2-agonist):

Two groups of six dogs each and one group of five dogs were premedicated as follows:

- Group 6 (5 µkg medetomidine IM): propofol dose 3.3 mg/kg (50% reduction)
- Group 7 (10 µkg medetomidine IM): propofol dose 2.2 mg/kg (67% reduction)
- Group 7.2 (10 µkg medetomidine IM): propofol dose 2.2 mg/kg (67% reduction)

Atipamezole reversal (30 ug IV) of group 7.2 occurred after 30 minutes of observations.

Atropine was given to all three groups (0.02 mg/kg) to prevent bradycardia.

Effects on anesthetic parameters of medetomidine with propofol induction:

The following tables show the individual duration of anesthesia and recovery times for dogs in groups 6, 7, and 7.2 in minutes:seconds.

Dog Number	Duration of Anes	Recovery Time
Group 6 (5 ug IM)		
87408	8 min 20 seconds	33'38"
86509	26'	37'23"
86444	18'47"	1'63"
87157	8'53"	24'12"
79120	0	13'24"
86452	17'40"	21'29"
Averages	13'16"	23'45"

Dog Number	Duration of Anesthesia	Recovery Time
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Group 7 (10 ug IM)

86339	2'	81'44"
79529	14'18"	49'
84921	6'	2'51"
81949	16'28"	54'46"
86461	20'40"	31'45"
87084	12'40"	48'34"
Averages	12'6"	44'49"

Dog Number	Duration of Anesthesia	Recovery Time*
------------	------------------------	----------------

Group 7.2 (10 ug IM)

79642	36'	2'10"
81949	26'	13'41"
82031	10'	30'20"
86444	15'	19'49"
84794	18'12"	19'31"
86991	10'	26'40"
Averages	19'12"	18'44"

* Medetomidine was reversed using atipamezole after 30 minutes resulting in much shorter recovery times compared to group 7.

Anesthetic duration was similar to dogs that received xylazine (see above). Recovery times were similar for xylazine and the lower dose of medetomidine (33'31", 23'45" respectively). Dogs that received the higher medetomidine dose experienced prolonged recovery times (44'49").

Group 6: The propofol dose for one dog in the 5 ug medetomidine group (#79120) was insufficient for anesthesia and intubation. Recovery time was also short for this dog (13.4 minutes) compared to the other dogs in the group.

Group 7: Two dogs in the 10 ug medetomidine group were not intubated due to insufficient anesthesia (79529 & 84921); one of these (84921) did not reach an adequate level of surgical anesthesia (determined by response to tail clamp). This dog also had a short recovery time (compared to others in group 7). The other dog (79529) experienced a delayed response until anesthesia.

Group 7.2: One dog was not sufficiently anesthetized for intubation (86991)

Recommendations:

The propofol dose of 3.3 mg/kg with 5 µkg of IM medetomidine premedication and the propofol dose of 2.2 mg/kg with 10 µkg of IM medetomidine premedication is sometimes insufficient to induce a surgical level of anesthesia and allow intubation. A higher routine initial propofol induction bolus dose of 3.3 mg/kg was recommended by the investigator if the larger propofol dose is not administered too rapidly. Slow administration (30-60 seconds) should prevent severe respiratory depression. Alternatively, the investigator recommends that an additional 1 mg/kg of propofol could be administered, but only if the induction dose is insufficient. However, these recommendations are not based on the results of this study. This method of induction has been used successfully in the literature and in the clinical trial (see below) using other premedicants (not medetomidine) with propofol when anesthesia has been insufficient for intubation. Note that additional low doses of propofol may cause apnea.

Physiological effects of medetomidine premedication with propofol induction:

As expected, medetomidine initiated a rise in BP. These changes were within acceptable limits. Increases in HR and respiratory depression due to propofol were also within acceptable limits. The use of oxygen enriched air was beneficial and increased oxygen saturation of hemoglobin. One dog in group 7 experienced ventricular tachycardia for approximately two minutes, elevated HR, and pulsas alternans (alternation in the height of the R and T waves). The investigator did not attribute this to the direct effect of premedication or anesthesia.

Atipamezole reversal of medetomidine:

Administration of atipamezole after the end of anesthesia (group 7.2) reversed the effects of medetomidine (including analgesia), reducing recovery time compared to the medetomidine group where sedation was allowed to continue (group 7).

Overall conclusion on groups 6, 7 & 7.2:

Physiologically, atropine, medetomidine, and propofol were compatible at the doses used in the study. Anesthetically, medetomidine preanesthesia to propofol anesthesia resulted in longer anesthesia times (anesthesia times similar to xylazine and oxymorphone). Recovery times were also longer because sedation from medetomidine lasted longer than propofol anesthesia, especially at the higher medetomidine dose. Longer recovery times were reversible using atipamezole. Apnea occurred infrequently and recoveries were smooth and safe. Insufficient anesthesia during intubation may occur using lowered propofol doses and IM medetomidine preanesthesia.

Analgesics - Opioid Agonist, Opioid Agonist/Antagonist:

Two groups of six dogs each were premedicated as follows:

- Group 5 (oxymorphone, opioid agonist): propofol dose reduced to 3.3 mg/kg
- Group 15 (butorphanol, opioid agonist/antagonist): propofol dose reduced to 4.4 mg/kg

All 12 dogs were anesthetized with evidence of analgesia (as determined by oximeter probe on tongue).

The following table shows average values in minutes for the duration of anesthesia and recovery times for groups 5 and 6 compared to results from Phase I of the dose determination study.

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Group	Duration of Anesthesia	Recovery Time
Phase I (propofol only)	6.53 min	13.90
5 (oxymorphone)	10.57	52.2
15 (butorphanol)	10.6	25.9

Longer anesthesia times and much longer recovery times were seen using oxymorphone with 50% the propofol dose (3.3 mg/kg). Elevated RR was seen following premedication with oxymorphone (and panting) prior to the administration of propofol. This effect is a reflection of the opioid agonist itself.

Butorphanol followed by a lower propofol dose (4.4 mg/kg) lowered respiratory rates. Oxygen saturation decreased with both premedicants, but to a greater degree with oxymorphone; however, dogs responded satisfactorily in both groups to supplemental oxygen.

HR decreased after administration of both premedicants, then increased following induction with propofol. BP increased after premedication, then decreased following propofol (lowest at 10 minutes after propofol). BP remained at acceptable levels and dogs did not require treatment for hypotension.

Analgesia lasted longer using oxymorphone compared to butorphanol as determined by toleration of the oximeter probe on the tongue (15 min butorphanol, 35 min oxymorphone).

Conclusion:

Propofol requirements were reduced by premedication with analgesics. Both duration of anesthesia and recovery times were increased, depending on the premedicant. Analgesia was increased with some premedicants compared to using propofol alone, especially with oxymorphone.

Tranquilizer and Analgesic (acepromazine, butorphanol):

One group of six dogs (group 16) was premedicated with acepromazine and butorphanol, followed by propofol induction at 3.3 mg/kg (50% decrease in induction dose).

The use of a tranquilizer and an opioid results in neuroleptanalgesia. More profound analgesia is seen than with the use of either premedicant alone (less response to tail cross clamp). The use of these premedicants also greatly reduced the dose of anesthetic that was needed. The duration of anesthesia and recovery time are also prolonged as seen in the following table of average values:

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Group	Duration of Anesthesia	Recovery Time
Phase I (propofol only)	6.53 min	13.90 min
16 (ace, butorphanol)	15.14	51.6
3 (acepromazine)	9.23	25.83
15 (butorphanol)	10.6	25.9

Duration of anesthesia and recovery time were both increased when the two premedicants were used in conjunction, compared to using butorphanol (group 15) or acepromazine (group 3) as the sole premedicant.

The use of both premedicants also had more profound cardiovascular effects than the use of either premedicant alone. Lower BP continued longer in group 16 (for 45 minutes). No adverse effects associated with hypotension occurred.

Four of six dogs experienced apnea and received oxygen supplementation following induction with propofol following acepromazine/butorphanol premedication. Four of six dogs also experienced apnea following induction with butorphanol/propofol; however, the propofol dose was higher. Apnea was not as common in the acepromazine/propofol group (one in five dogs).

Conclusion:

The use of acepromazine/butorphanol prior to propofol is more likely to cause respiratory depression than either single premedicant. This combination also lengthens anesthesia, recovery, and provides more profound analgesia.

The results described for the dose groups above showed that the use of propofol for induction of anesthesia, under clinically relevant conditions utilizing preanesthetic agents that are likely to be used in the field, is safe and effective when dosage levels of propofol have been appropriately adjusted.

Anesthesia Maintenance with Propofol:

Three groups of six dogs were anesthetized as follows:

Group	Premedicants	Propofol Induction
12	atropine 0.02 mg/kg IM	6.6 mg/kg IV (over 60 sec)
13	atropine 0.02 mg/kg IM acepromazine 0.1 mg/kg IM	4.4 mg/kg IV (over 40 sec)
14	atropine 0.02 mg/kg IM medetomidine 10 µg IM	2.2 mg/kg IV (over 20 sec)

Atropine was given 20 minutes before anesthetic induction. Acepromazine or medetomidine were given 15 minutes before induction. Maintenance doses of propofol (1.1 mg/kg IV) were given as needed for 30 minutes. RR, CO₂, HR, BP, and body temperature were recorded. EEG and oxygen saturation measurements were begun at 2 minutes after propofol induction.

Anesthesia Effects:

In these three groups, neurologically equivalent levels of anesthesia were established using propofol as determined by electroencephalographic analyses. Decreased amplitude can be correlated with a neurologically surgical plane of anesthesia (Short, C. The effects of selective alpha-2-adrenoreceptor agonists on cardiovascular and pulmonary functions and brain wave activity in horses and dogs. Veterinary Practice Publishing Company, Santa Barbara, CA (1991), p. 13). The EEG recordings coupled with a subjective pain stimulus (tail clamp) indicated that adequate equipotent anesthesia was achieved in all three groups.

The following table shows average values in minutes for the duration of anesthesia and recovery times for groups 12, 13, and 14 compared to results from Phase 2 (maintenance) of the dose determination study.

Groups	Duration of Anesthesia*	Recovery Time
Phase 2 (propofol only)	32.1 minutes	15.83 minutes
group 12 (atrop, prop)	33.5	9.5
group 13 (atrop, ace, prop)	32.1	16.5
group 14 (atrop, medet, propofol)	38.9	32.9

* Dogs received maintenance boluses of propofol for 30 minutes.

Recovery times were comparable between groups 12 and 13, and much longer in group 14. Recovery times reflect the influence of the premedicant that was used.

The following table shows the influence of preanesthesia on propofol maintenance requirements.

Group	No. of Repeat Doses	Mean Minutes Between Doses
12	5.8 (4-8 range)	6:05 (min/sec)
13	5.7 (2-8)	7:21
14	4.5 (3-8)	10:15

The frequency of supplemental doses reflects the effects of premedication. Premedication with medetomidine results in longer intervals between maintenance doses and longer recovery times compared to pretreatment with acepromazine or atropine alone.

Three (of six) dogs in the medetomidine group could not be intubated using 2.2 mg/kg propofol IV, but were intubated after an additional 1.1 mg/kg propofol was administered (see additional comments

concerning insufficient anesthesia using medetomidine and propofol under the discussion of groups 6, 7, and 7.2 above).

Physiological Parameters:

Cardiovascular: Atropine increased the HR in all three groups, peaking at the time of propofol induction (15 minutes after atropine administration) and subsequently declining. BP declined slightly after induction in groups 12 and 13. No differences were noted in BP between these two groups.

BP was continuously elevated during the entire anesthetic period in group 14, peaking at 10-15 post-propofol and then slowly declining. Medetomidine administration causes a rise in BP (initial vasopressor response due to vasoconstriction). The bradycardia that is seen in dogs receiving medetomidine alone is probably a reflex response to this hypertension. Since atropine prevented this bradycardia, the hypertension was prolonged. The investigator believes that BP in this group would have returned to baseline levels within 30 minutes if atropine had not been administered as well as medetomidine. Cardiovascular problems associated with the use of atropine in conjunction with medetomidine are partially discussed on the medetomidine label under Precautions.

RR: RR were elevated in group 12, and stable in groups 13 and 14. One dog in group 12 experienced apnea after propofol induction. Apnea was resolved within six minutes using oxygen and manual intermittent positive pressure ventilation (IPPV). Other significant drops in RR of clinical concern were not observed.

Oxygen saturation: All dogs received oxygen since all oxygen saturation levels decreased below 90%; therefore, the values reflect the use of oxygen as needed to maintain saturation at greater than 90%. Initial oxygen saturation levels indicate that medetomidine treated dogs experienced greater respiratory depression.

Body Temperature: All dogs showed an expected drop in temperature by an average of 2.3 deg.F.

Anesthesia Maintenance with Inhalant Anesthetics:

Three groups of six dogs each were anesthetized as follows:

- Group 9: propofol induction dose 6.6 mg/kg, isoflurane maintenance
- Group 10: propofol induction dose 6.6 mg/kg, methoxyflurane maintenance
- Group 11: propofol induction dose 6.6 mg/kg, halothane maintenance

Dogs were induced with propofol, intubated, and breathed oxygen until the 2 minute post-propofol measurements were made. Dogs were then maintained on inhalant anesthetics for 30 minutes as follows:

- Methoxyflurane: Ohio #8 in-circle vaporizer
- Isoflurane and Halothane: precision out-of-circle vaporizers

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In addition to the other clinical and physiological measurements, electroencephalograms (EEGs) were also recorded for these three groups. EEG results demonstrated a neurologically surgical plane of anesthesia with the use of the inhalant anesthetics. This parameter did not provide any relevant data with regard to propofol and is therefore not discussed in this FOI Summary.

Anesthetic Effects:

The following table shows average values in minutes for the duration of anesthesia and recovery times for groups 9, 10, and 11.

Groups	Duration of Anesthesia	Recovery Time
group 9 (isoflurane)	39.1 minutes	10.1 minutes
group 10 (methoxyflurane)	46.5	5.4
group 11 (halothane)	43.16	5.7

Dogs in groups 9, 10, and 11 received inhalant maintenance anesthesia for 30 minutes. Induction and intubation was achieved in all three groups. There was a problem regarding the transition from propofol induction to methoxyflurane anesthesia. All dogs partially aroused from anesthesia before they stabilized on methoxyflurane (2-5 minutes after propofol injection). This problem could probably have been avoided if methoxyflurane had been administered immediately after induction (instead of waiting until the two minute propofol measurements were made). Recovery from propofol was too rapid to allow for inhalation of adequate concentrations of methoxyflurane. This was not a problem with isoflurane or halothane. Once adequate concentrations had been inhaled, anesthesia was satisfactorily maintained in the methoxyflurane group.

Physiological Parameters:

HR: As expected, HR increased following propofol induction, then decreased during inhalant maintenance, with no problems noted.

BP: Mean arterial BP was higher during propofol anesthesia than with the inhalants. BP were acceptable during inhalant maintenance and responded to adjustment of the inhalant concentrations.

RR: The most profound respiratory depression was seen immediately after propofol induction.

Oxygen saturation was slightly reduced after propofol, and was corrected and stabilized after oxygen and inhalant administration. Some CO₂ accumulation was observed during methoxyflurane anesthesia; this was a response to both propofol and methoxyflurane.

Conclusion on Groups 9, 10, and 11:

Compatibility of propofol with the three inhalant anesthetics was demonstrated. It is probable that induction and adequate maintenance anesthesia using methoxyflurane will be possible under field conditions when the inhalant is administered immediately after propofol induction and preanesthetics are used. Physiological parameters and recovery times were satisfactory. Based on these results, propofol is safe and effective for induction of anesthesia that will be maintained by an inhalant.

Adverse Reactions During Compatibility Study:

No dogs died during the study. No uncontrollable adverse reactions were observed. All animals received oxygen routinely and IPPV was available. Apnea occurred infrequently and as expected was the most common adverse event (16 times in 102 anesthetic episodes).

Nine dogs could not be intubated because of insufficient anesthesia. All of these dogs (9 of 24) received IM medetomidine as a preanesthetic prior to the lowest propofol induction dose (2.2 mg/kg). Inability to intubate occurred in all four medetomidine groups (6, 7, 7.2, and 14). An additional 1.1 mg/kg of propofol allowed intubation to be achieved easily in all instances.

Other minor adverse reactions occurred, included paddling, muscle tremors, muscle rigidity, panting, and slow recovery. Slow recoveries were related to premedication, not to propofol.

One dog in group 7 (medetomidine, 10 µg IM) experienced ventricular tachycardia for approximately two minutes, elevated HR, and pulsus alternans (alternation in the height of the R and T waves). There was nothing in the dog's clinical records to explain the abnormality and there is no reason to associate its occurrence with either propofol or the premedicants.

C. CLINICAL TRIAL UNDER FIELD CONDITIONS WITH PROPOFOL IN DOGS:

Sponsor Monitor:

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4. Colorado State University (CSU)

Dr. Jamie Gaynor

Dr. Etta Wertz

5. Community Veterinary Hospital (CVH)

Dr. William Grant II

Dr. Grace Matsuura

6. Hoffman Estates Animal Clinic (HEAC)

Dr. Ann Brooks

Dr. Joy Dvorak

Dr. Jeffrey House

7. Kildaire Animal Medical Center (KAMC)

Dr. Nick Ashford

Dr. Christine Boyd

Dr. Michele Karl

Dr. Dianna Shattuck

Dr. John Strasser

8. Michigan State University (MSU)

Dr. George Bohart

Dr. Donald Sawyer

9. Ralston Veterinary Clinic (RVC)

Dr. Allan Erickson

Dr. Norman B. Jernigan

10. Vernon Hills Animal Hospital (VHAH)

Dr. Molly McCullough

Dr. Cheryl Roge

11. West Bay Animal Hospital (WBAH)

Dr. Daniel Simpson

Study Dates: April, 1995 to September, 1995

Objectives:

1. To evaluate the efficacy of propofol when administered:
 - a. as the sole anesthetic agent in dogs (induction & maintenance).
 - b. in conjunction with preanesthetic agents in dogs.
 - c. for induction of anesthesia with subsequent maintenance by inhalant anesthetics.
2. To confirm the safety of propofol under clinical field conditions and identify the need for special label precautions.

Study Design:

The study included 325 dogs that were presented to veterinarians in private practice or at veterinary teaching hospitals for surgery and/or other procedures that required anesthesia. The study population was divided into three major treatment classifications:

1. propofol as the sole anesthetic, either as a single injection for induction, or with repeated administrations for maintenance anesthesia,
2. propofol induction in conjunction with various preanesthetics (acepromazine, oxymorphone, butorphanol, xylazine, and acepromazine/butorphanol), maintained if necessary with propofol or inhalant anesthetics,
3. propofol induction with subsequent maintenance by inhalant anesthetics (halothane or isoflurane).

Dogs were placed into treatment classifications by the investigator based on the length of the procedure, the type of surgery, the test facility capability, and occasionally the temperament of the dog. Intravenous catheters were utilized for 231 cases during the study.

Data recorded included information on the patients and procedures, objective and subjective anesthetic performance (ease of induction, duration and nature of anesthesia, duration and nature of recovery, overall satisfaction), physiological parameters (respiration rate, pulse rate, blood pressure), and adverse reactions.

A varied number of breeds (approximately 70) and crossbreeds were represented. The dogs ranged in age from two months to 16 years and in weight from 1.8 - 77.7 kilograms. The study included 180 males (intact and castrated), 144 females (intact and spayed), and one where the sex was not indicated. There were instances when the same dog was anesthetized more than one time during the study, and these were considered a separate case each time. Of the 325 anesthetic episodes, 313 dogs were anesthetized once. Five dogs were used more than once, representing twelve anesthetic episodes.

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The most prevalent concomitant therapies were those involving heartworm prevention. Other concomitant therapies included atropine, hydrazine, phenobarbital, and chloramphenicol.

Physical Status of Study Dogs:

The following table shows the number of dogs in each health classification as determined by physical examination (status is based on the American Society of Anesthesiologists/ASA rating):

Induction Regime	# Dogs	ASA 1	ASA 2	ASA 3	ASA 4
propofol only	42	30	9	3	-
propofol/acepromazine	47	41	5	1	-
propofol/oxymorphone	48	38	8	2	-
propofol/xylazine	41	38	3	-	-
propofol/butorphanol	24	17	5	2	-
prop/butorph/aceprom	24	22	1	1	-
propofol/halothane	51	40	10	1	-
propofol/isoflurane	48	44	2	1	1
totals	325	270	43	11	1

Dogs in the study were classified as ASA 1-4 with the following conditions:

ASA 1 (83%) = healthy without any apparent underlying condition.

ASA 2 (13%) = geriatric obesity, parasites, dehydration, or infection (n=21); heart murmurs (n=4); fever/infection (n=4); chronic gastrointestinal (GI) problems (n=2); recent wounds/injuries (n=2); pregnancy (n=2); dislocated hip (n=1); obesity only (n=1); previous recent surgery (n=1); idiopathic epilepsy (n=1); immune mediated or autoimmune gingivitis (n=1); possible embolism (n=1); hyperadrenocorticism (n=1); and mammary tumors (n=1).

ASA 3 (3%) = geriatric neoplasia, obesity, metabolic disease (n=4); chronic diabetes (n=1); heartworm disease (n=1); metabolic disease (n=1); pyelonephritis with grade III/IV systolic heart murmur and enlarged pancreas (n=1); severe intestinal parasitism with depression (n=1); and a slightly febrile and icteric dog with a testicular mass and enlarged prostate (n=1).

ASA 4 (one dog) = gastric dilatation and volvulus.

Procedures:

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The most common procedures for which dogs were admitted to the study were castrations, ovariohysterectomies, dental cleanings, tumor removals, wound repair and X-rays. Multiple procedures were completed during anesthesia in some dogs. One cesarean section was accomplished (xylazine/propofol/isoflurane), one total hip replacement (acepromazine/butorphanol/propofol/isoflurane), and one gastric dilatation/volvulus surgery (propofol/isoflurane).

The following table lists the procedures conducted, concomitant therapies, site, number of dogs (n), temperament (temp.) types (C=calm; N=nervous, excited; A=aggressive; and D=depressed), and the duration (mean and range) for procedures for each regimen (min:sec or hr:min:sec):

Regimen, (n), Procedure Duration (Mean & Range)	Site	Temperament & number	Procedure & number	Concomitant Therapy & number

Propofol Only n=42 7:50 0:06-23:24	BAC	C 20	X-rays plus	10 Interceptor (milbemycin oxime) 3
	RVC	N 16	Aspirates/biopsies	5 Lactated Ringers 3
	VHAH	A 1	Dental Plus	4 Heartgard (ivermectin) 2
	HEAC	D 4	Castration	3 Ophthaine 2
	BVC	N+A 1	Suture/wound repair	3 Paramite Dip 1
	AEC		Mass removal	3 Cortaba 1
	CSU		Pedicure plus	2 Flocillin 1
	CVH		Oral Exam	1 Baytril 1
	MSU		Ear lavage	1 Banamine 1
			CSF collection	1 Gentocin o.o. 1
			Hardarian gland removal	1 DA2PPVL 1 Flagyl 1
			Avulsed toenail removal	1 Meclofenamic acid 1 Aminophylline 1
			Cast leg	1 Phenylpropanolamine 1
			Porcupine quill removal	1 Thyrozine 1 Cefazolin 1
			Fish hook removal	1 Cefoxitin 1
			Grass awn removal	1
			Flush and infuse anal glands	1
			Tarsorrhaphy	1
Propofol	RVC	C 5	X-rays plus	5 Heartgard Plus 2
Acepromazine/	VHAH	N 4	Pedicure plus	2 Program (lufenuron) 1

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No maintenance CVH	Suture removal	1	Aspirin	1
n= 9 5:04	Remove piece of	1		
0:01-8:10	lacerated pad			

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Regimen, (n), Procedure Duration (Mean & Range)	Site	Temperament & number	Procedure & number	Concomitant Therapy & number
Propofol	RVC	C 6	Castration	4 Aspirin 3
Acepromazine/	VHAH	N 7	Dental/extractions	4 Cephalexin 2
Propofol	BVC	A 1	X-rays/exams	2 Interceptor 1
maintenance	CVH		Tumor/cyst removal	2 Program 1
n=14 11:25			Bandage and wound	2 Dexamethasone 1
1:49-31:18			therapy	Filaribits Plus 1
				Gentamicin 1
Propofol	BVC	C 4	Spay	4 Atropine 1
Acepromazine/	CSU	N 7	Dental/extractions	3 Amoxicillin 1
Halothane	CVH	C+N 2	Castration	1 Interceptor 1
maintenance	MSU		Dewclaw removal	1 Soloxine 1
n=13 44:08			Bronchoscopy	1
9:27-2:29:39			Wedge Trochlear.	1
			Mass excision	1
			Tarsal arthrodesis	1
Propofol	RVC	C 3	Castration	5 Heartgard 1
Acepromazine/	VHAH	N 7	Dental plus	2 Program 1
Isoflurane	CVH	A 1	Aural hematoma	2 Thyrozine 1
maintenance			Tonsillectomy	1
n=11 22:57			Spay	1
6:23-53:55				

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Regimen, (n), Procedure Duration (Mean & Range)	Site	Temperament & number	Procedure & number	Concomitant Therapy & number
Propofol	RVC	C 5	X-rays +/- exam	6 Heartgard 1
Oxymorphone/	CSU	N 4	Flush wound	1 Cephalexin 1
No maint.	CVH	D 1	Tumor removal	1 Prednisone 1
n=10 4:47	MSU		Dental	1
0:54-13:37			Nail trim	1
Propofol	RVC	C 4	Dental plus	3 Keflex 1
Oxymorphone/	CSU	N 8	Castration	1 Oxycillin 1
Propofol	CVH		Mass removal	1
maintenance	MSU		Ear exam/cleaning	1
n=12 23:38			X-ray	1
10:33-1:04:52			Bronchoscopy	1
			Wound closure	1
			Vaginal endoscopy	1
			Bandage change/ suture removal	1
			Colonoscopy	1
Propofol	CSU	C 5	X-rays plus	3 Heartgard 1
Oxymorphone/	CVH	N 8	Castration plus	3
Halothane	MSU		Dental	2
maintenance			FLIT	1
n=13 1:20:42			Tumor removal	1
9:11-4:18:32			Spay	1
			T-L myelogram	1
			Skin biopsy	1
Propofol	RVC	C 4	Dental plus	4 Thyrozine 2
Oxymorphone/	CSU	N 8	Castration plus	2 Amoxicillin 1
Isoflurane	CVH	D 1	Spay	1 Interceptor 1
maintenance	MSU		Bronchoscopy	1 Proanthazone 1
n=13 55:08			Biopsy	1 Adequan 1
13:27-2:17:38			Polyp removal	1 Ascriptin 1
			Oro-nasal fistula repair	1 Clindamycin 1
			Endoscopy	1 Baytril 1
			Modified	1 Antirobe 1
			retinacular	1 Clavomox 1
				Tagamet 1

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				imbrication		Reglan	1
						Carafate	1
Regimen, (n), Procedure Duration (Mean	Site	Temperament & number	Procedure & number			Concomitant Therapy & number	
Propofol	BAC	C 2	Dental plus	4	Heartgard	1	
Xylazine/ No	BVC	N 5	Ear canal lavage	3	Interceptor	1	
maintenance	RVC	A 3	OFA X-ray	1			
n=10 11:31	CSU		Vaginal cytology	1			
2:15-29:47			Nail trim	1			
Propofol	BAC	C 3	Dental	3	Levothyroxine	1	
Xylazine/	RVC	N 7	Castration	3			
Propofol	AEC		Porcupine quill	1			
maintenance	CSU		removal				
n=10 14:40	MSU		Toe nail removal	1			
5:32-42:52			X-rays	1			
			Lumpectomy	1			
Propofol	BVC	C 4	Castration	3	Interceptor	3	
Xylazine/	CSU	C 6	Spay	2	Amoxicillin	3	
Halothane	MSU		Orthopedic surgery	2	Baytril	1	
maintenance			Dental	1	Lactated Ringers	1	
n=10 48:09			Tumor removal	1	and dextrose		
21:40-2:43:40			Ear biopsy	1	Program	1	
Propofol	BAC	C 5	Dental	4	Amoxicillin	1	
Xylazine/	AEC	N 6	Orthopedic surgery	2	Prednisone	1	
Isoflurane	CSU		Cesarean section	1	Ascriptin	1	
maintenance	MSU		Laceration repair	1			
n=11 49:00			Mass removals	1			
7:29-2:32:13			CSF tap plus	1			
			X-rays	1			
Propofol	RVC	C 3	X-rays	4	None		

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Butorphanol/ No CVH	N 6	Castration	2
or Propofol		Extract teeth	1
maintenance n=9		Laceration repair	1
6:28 1:07-12:47		Remove wire	1

Regimen, (n), Procedure Duration (Mean & Range)	Site	Temperament & number	Procedure & number	Concomitant Therapy & number
Propofol	BVC	C 6	Dental plus	3 Amoxicillin 2
Butorphanol/	CSU	N 3	Spay	3 Filaribits Plus 1
Halothane	CVH	A 1	Castration	1 0.9% NaCl 1
maintenance			Cyst excision	1 Lactated Ringers 1
n=10 50:13			Gastric tube	1 Baytril 1
8:20-2:24:15			placement	Ampicillin 1
			Otic lavage	1 Adequan 1
Propofol	RVC	C 5	Dental plus	2 None
Butorphanol/			Castration	1
Isoflurane			Spay plus	1
maintenance n=5			Tumor removal	1
52:25				
12:12-1:21:44				
Propofol	RVC	C 5	Castration	3 Cephalixin 1
Butorphanol,	CVH	N 2	X-rays	2
Acepromazine/			Nail trim	1
No or propofol			3rd eyelid flap	1
maintenance n=7			repair	
8:59 4:30-11:51				
Propofol	BVC	C 2	Castration plus	5 Amoxicillin 5
Butorphanol,	CSU	N 9	Spay	2 Interceptor 2
Acepromazine/			X-rays	2 Atropine 1
Halothane			Tumor removal	1 Lactated Ringers 1
maintenance			Examine mouth	1 Gentamicin 1
n=11 53:42				
8:01-2:10:37				
Propofol	RVC	C 2	Castration	2 Heartgard 2

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Butorphanol, acepromazine/ Isoflurane maintenance n=6 28:37 12:28-47:19	MSU	N 4	Dental Spay Total hip replacement (THR)	2 1 1	Program Ampicillin	1 1
Regimen, (n), Procedure Duration (Mean & Range)	Site	Temperament & number	Procedure & number		Concomitant Therapy & number	
Propofol Only/ Halothane maintenance n=51 32:12 4:48-1:59:03	KAMC HEAC BVC CVH	C 22 N 29	Dental plus Spay plus Castration plus Tumor removal Orthopedic surgery X-rays Anal gland removal Suture repair Bandage/recast Digit amputation	18 10 10 4 4 1 1 1 1 1	Interceptor Flocillin Heartgard Lactated Ringers Program Thyrozine Derm Caps Cephalexin Soloxine Filaribits Plus Amoxicillin Ascriptin Hydroxyzine Atropine Phenobarbital	20 10 9 4 3 3 2 2 2 2 2 1 1 1 1
Propofol Only/ Isoflurane maintenance n=48 26:38 1:18:45	WBAH RVC VHAH HEAC AEC CVH	C 31 N 16 D 1	Castration plus Dental plus Spay plus Tumor removal plus Laceration repair Aural hematoma Orthopedic exam 3rd eyelid flap repair GDV (gastic dila- tation volvulus surgery	15 12 11 4 2 1 1 1 1 1 1	Interceptor Flocillin Lactated Ringers Program Heartgard Prednisone Cefazolin Amoxicillin Paramite dip Phenobarbital Chloramphenicol Cholodin Potassium bromide Cytomel	10 7 5 2 2 2 1 1 1 1 1 1 1 1

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Digoxin	1
Thyrozine	1
Aminophylline	1
Enacard	1

Induction of Anesthesia:

Premedication Treatment Groups:

Lists of the premedication, number of animals treated with each premedication, route of delivery, mean dose and dose range for each premedication, the mean time and range of times between premedication and propofol induction are shown in the following table:

Preanesthetic Agent	Route of Delivery		Mean Dosage (mg/kg)	Mean Interval to Propofol (minutes)
n	IM	SQ	Dosage Range (mg/kg)	Range
	n	n		
Acepromazine	20	27	0.1	49
47			0.02-0.77	9-154
Oxymorphone	24	24	0.1	52
48			0.09-0.11	13-295
Xylazine	30	11	0.52	36
41			0.33-1.1	0-117
Butorphanol*	14	10	0.2	40
24			0.13-.26	10-65
Acepromazine/ Butorphanol	15	9	0.15	
			0.04-0.70	43
24			0.2	15-83
			0.15-0.22	

*The safety of general anesthesia with propofol when used in conjunction with butorphanol premedication was evaluated. However, butorphanol is not approved as a preanesthetic in dogs.

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Most dogs received propofol between 20 and 60 minutes after premedication during the study. A wide range of time between premedication and administration of propofol affects the dosage and duration of propofol necessary for induction.

Premedicant doses are frequently lower than their label doses (see Thurmon et al., 1996, under References). The use of the anticholinergic atropine was at the discretion of the investigators. Atropine was administered prior to propofol induction in 56 % of the cases.

The mean propofol induction doses (and ranges) for each treatment group and the mean dose rates of administration (and ranges) are shown in the following table:

Regimen	n	Propofol Dose (mg/kg) Mean Range	Propofol Dose Rate (mg/kg/min) Mean Range
Propofol Only	136	6.31 3.59-8.34	6.77 2.71-39.45
Acepromazine/ Propofol	46	4.19 2.64-5.87	3.74 1.25-5.87
Oxymorphone/ Propofol	47	3.31 1.43-5.90	2.92 1.19-4.95
Xylazine/ Propofol	41	2.75 1.94-8.01	2.34 0.55-7.02
Butorphanol/ Propofol	24	4.71 3.76-7.15	4.50 2.75-6.36
Acepromazine/ Butorphanol/ Propofol	24	2.37 1.52-4.42	2.27 1.45-4.42

Ease of Induction Scores were defined as follows:

Excellent = smooth, easily intubated

Good = needed up to 25% more propofol; otherwise smooth

Fair = required 25-50% more propofol; slight jaw tone, some movement

Poor = required more propofol; difficult to intubate, great amount jaw tone

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Induction using propofol alone or with premedicants was mostly scored as excellent or good.

Scores	Propofol only n=136	Ace/ Propofol n=46	Oxymor/ Propofol n=47	Xylazine/ Propofol n=41	Butorph/ Propofol n=24	Ace/But/ Propofol n=24
Excellent	126 (93%)	44 (96%)	44 (94%)	27 (65%)	17 (70%)	20 (83%)
Good	7 (5%)	2 (4%)	2 (4%)	6 (15%)	5 (21%)	2 (8%)
Fair	3 (2%)		1 (2%)	3 (7%)	1 (4%)	2 (8%)
Poor				5 (12%)	1 (4%)	

Xylazine premedication resulted in 8 cases (of 41) as fair or poor. In the clinical trial protocol, the propofol dose following xylazine premedication was recommended as 2.2 mg/kg. Based on the results of the clinical trial, it may be necessary in some cases to increase the propofol dose to 3.3 mg/kg in order to improve induction. Based on these data, the labeling recommendation has been altered to a propofol dose of 2.2 to 3.3 mg/kg when xylazine is used as a premedicant. The time interval between premedication and propofol dosing is a key factor with this premedicant. The longer the interval between premedication and propofol administration, the higher the amount of propofol that may be necessary for induction.

The mean propofol induction doses with the remaining premedication regimens were consistent with the recommended protocol doses. Based upon these data and results from previous clinical studies, ranges for propofol induction with various premedications in a clinical environment have been established (see the Induction Dosage Guidelines table).

Propofol Maintenance anesthesia:

An induction dose of propofol provided anesthesia for 4:32 to 10:30 (min:sec), depending on the anesthetic regime. An incremental or maintenance dose of propofol provided anesthesia for 3:55 to 7:23, varying according to premedicant.

A comparison of the mean induction dose intervals (min:sec) and mean induction doses (mg/kg) with the mean duration of anesthesia and doses for all maintenance intervals is shown in the following table:

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Induction Regimen	Induction Anesthetic Duration (min:sec) Mean Induction Dose (mg/kg) n	Mean Duration for Maintenance Intervals Only Mean Dose (mg/kg) n
Propofol Only	6:52 6.47 40	6:26 1.48 48
Acepromazine/ Propofol	5:38 4.23 22	3:55 1.21 49
Oxymorphone/ Propofol	6:49 3.35 21	6:11 1.12 48
Xylazine/ Propofol	10:30 2.50 19	7:23 1.03 23
Butorphanol/ Propofol	4:34 4.49 9	4:14 1.45 11
Acepromazine/ Butorphanol/ Propofol	4:32 2.11 7	6:43 1.02 11

The mean propofol maintenance doses were consistent with the recommended label doses for propofol as used with premedicants (1.1 mg/kg), except for butorphanol. Butorphanol required 1.45 mg/kg of propofol (see maintenance induction guideline table under dosage and administration above).

Mean maintenance doses for propofol alone were 1.48 mg/kg, within the label recommended maintenance dose range of 1.1 to 3.3 mg/kg.

Maintaining surgical depth of anesthesia and avoiding the first plane of arousal during propofol maintenance anesthesia requires close attention. Several dogs showed signs of rapid anesthetic arousal. One investigator attempted a spay with propofol only, but depth of anesthesia was not sufficiently stable for the procedure and the dog was switched to an inhalant. However, several castrations were accomplished with propofol induction and maintenance only.

Anesthesia with Propofol Induction and Inhalant Maintenance:

As expected, the longest anesthetic episodes were maintained with inhalants rather than with propofol. Dogs were maintained with either isoflurane or halothane by changing vaporizer settings as necessary.

Instances occurred when the anesthetic duration following the induction dose of propofol was insufficient to complete transition to the inhalant. It may be necessary to increase initial vaporizer settings above those used with other induction anesthetics, in order to counterbalance the rapid recovery from propofol. Another alternative is to deliver a low maintenance dose of propofol. Several investigators administered small incremental doses of propofol during inhalant maintenance to rapidly deepen the plane of anesthesia, in addition to increasing vaporizer settings, resulting in two incidences of apnea. Apnea may also occur following a maintenance dose of propofol alone.

Overall Anesthetic Effectiveness:

Lists of the anesthetic effectiveness scores, and the mean and ranges of duration of anesthesia for all subregimens in the study are presented in the following table. Anesthetic effectiveness was subjectively scored as follows:

Excellent (E) = very good muscle relaxation, anesthesia completely adequate for procedure

Good (G) = not totally relaxed, but anesthesia sufficient for procedure

Fair (F) = unable to get good muscle relaxation, stayed light throughout procedure

Poor (P) = insufficient anesthesia for procedure

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Regimen	Anesthetic Effectiveness Scores				Percent with Scores of Excellent or Good
	E	G	F	P	
Propofol Only	29	10	3	9	3% (39 of 42)
Propofol/acepromazine, no maintenance	8	1			100% (9 of 9)
Propofol/acepromazine, propofol maintenance	5	7	2		85% (12 of 14)
Propofol/acepromazine, halothane maintenance	9	3			100% (12 of 12)
Propofol/acepromazine, isoflurane maintenance	11				100% (11 of 11)
Propofol/oxymorphone, no maintenance	5	4	1		90% (9 of 10)
Propofol/oxymorphone, propofol maintenance	11		1		92% (11 of 12)
Propofol/oxymorphone, halothane maintenance	11	2			100% (13 of 13)
Propofol/oxymorphone, isoflurane maintenance	11	2			100% (13 of 13)
Propofol/xylazine, no maintenance	9	1			100% (10 of 10)
Propofol/xylazine, propofol	8	2			100% (10 of 10)

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maintenance					
Propofol/xylazine, halothane maintenance	8		1		89% (8 of 9)
Regimen	Anesthetic Effectiveness Scores				Percent with Scores of Excellent or Good
	E	G	F	P	

Propofol/xylazine, isoflurane maintenance	9	2			100% (11 of 11)
Propofol/butorphanol, no or propofol maintenance	5	3	1		89% (8 of 9)
Propofol/butorphanol, halothane maintenance	7	2			100% (9 of 9)
Propofol/butorphanol, isoflurane maintenance	5				100% (5 of 5)
Propofol/butorphanol/ acepromazine, no or propofol maintenance	5	2			100% (7 of 7)
Propofol/butorphanol/ acepromazine, halothane maintenance	6	2	1		89% (8 of 9)
Propofol/butorphanol/ acepromazine, isoflurane maintenance	6				100% (6 of 6)
Propofol only, Halothane maintenance	36	11	3	1	92% (47 of 51)
Propofol only, Isoflurane maintenance	41	6	1		98% (47 of 48)

Recovery:

The following table shows the mean times and ranges from the end of anesthesia to head lift, sternal recumbency, and standing, along with recovery scores.

Recovery was subjectively scored as follows:

- Excellent = completely smooth recovery
- Good = smooth recovery with minor paddling or tremors
- Fair = paddling, thrashing when moving, sensitive to noise
- Poor = rough recovery, vocalization, opisthotonus, clonic/tonic seizures

Means and ranges for head lift, sternal and standing intervals (hr:min:sec), and recovery comments are listed by drug regimens. Regimens are divided by either propofol, halothane, or isoflurane maintenance.

Regimen	Head Lift	Sternal	Standing	Recovery			
	Mean Range	Mean Range	Mean Range	E	G	F	P
Propofol Only	3:38 0:00-13:16	5:27 0:00-25:10	15:41 1:17-1:43:48	29	10	2	1
Propofol, halothane maintenance	3:02 0:00-12:06	6:08 0:00-27:08	16:00 3:12-43:13	34	11	4	1
Propofol, isoflurane maintenance	2:06 0:00-19:19	3:10 0:00-31:53	10:59 0:03-1:11:38	36	10	2	
Propofol/ acepromazine, propofol or no maintenance	5:25 0:13-39:04	8:57 0:29-1:02:40	17:03 2:40-1:15:17	16	4	2	1
Propofol/	7:14	16:15	27:12	10	2		

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acepromazine, halothane maintenance	0:00-28:53	0:43-1:08:25	4:00-1:08:25	
Propofol/ acepromazine, isoflurane maintenance	2:52 0:12-5:04	4:31 1:20-10:52	16:06 6:38-33:57	7 4

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Regimen	Head Lift Mean Range	Sternal Mean Range	Standing Mean Range	Recovery Comments			
				E	G	F	P
Propofol/ oxymorphone, none or propofol maintenance	1:38 0:00-9:11	2:56 0:01-10:35	9:27 0:28-16:02	19	1	1	1
Propofol/ oxymorphone, halothane maintenance	7:49 0:00-35:16	11:26 0:00-38:36	24:17 1:40-1:22:08	8	2	2	
Propofol/ oxymorphone, isoflurane maintenance	2:02 0:00-10:59	6:02 0:00-31:22	16:17 0:22-31:22	11	2		
Propofol/ xylazine, no or propofol maintenance	5:59 0:00-18:39	6:48 0:20-18:51	12:27 1:15-35:19	18	2		
Propofol/ xylazine, halothane maintenance	9:53 0:00-53:18	10:30 0:00-53:18	15:34 0:00-53:18	9			
Propofol xylazine, isoflurane maintenance	4:07 0:00-14:42	5:21 0:00-19:07	12:40 1:09-52:05	8	2		
Propofol/ butorphanol, no or propofol maintenance	3:47 0:00-13:52	6:10 1:27-17:49	11:27 2:00-24:00	8	1		
Propofol/ butorphanol,	4:13 0:00-9:55	17:28 0:00-1:44:06	37:42 7:37-1:58:16	7	2		

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halothane maintenance									
Regimen		Head Lift	Sternal	Standing					Recovery
		Mean	Mean	Mean					Comments
		Range	Range	Range					E G F P
Propofol/ butorphanol, isoflurane maintenance	1:44 0:52-2:58		4:04 1:12-8:16	11:03 6:25-15:41				2 2 1	
Propofol/ butorphanol/ acepromazine, no or propofol maintenance	4:20 1:10-8:16		9:25 4:14-20:01	19:29 7:10-36:29				7	
Propofol/ butorphanol/ acepromazine, halothane maintenance	5:05 0:00-15:36		10:07 0:00-20:53	1:54:55 6:20-7:12:55				6 3	
Propofol/ butorphanol, acepromazine, isoflurane maintenance	3:59 0:53-10:45		9:19 2:03-17:41	26:56 7:43-59:38				2 4	

93% (114 of 123) of dogs that received propofol for maintenance were classified as excellent or good recoveries. 95% of dogs (184 of 194) of dogs maintained with inhalants were classified as excellent or good.

Dogs that received repeated doses of propofol for maintenance anesthesia did not have increased recovery times indicating that the effects of propofol were not cumulative. Dogs that received repeated propofol maintenance doses had similar recovery times (15:43) compared to those receiving a single dose (12:21), also indicating that the effects of propofol were not cumulative.

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Some dogs that received acepromazine/butorphanol premedication experienced profound sedation prior to propofol induction (9 of 24). Prolonged, sluggish recoveries resulted as well in some dogs that received this premedication regimen (see table above). It is recommended when using this regimen, that the dosage of one or more of the products (acepromazine, butorphanol, or propofol) may be further reduced to lessen pre-anesthesia sedation or prolonged recovery.

Physiological Parameters:

Pulse Rate and Respiratory Rate:

The following table compares the physical exam, pre-induction, induction, and pre-procedure mean pulse rate (PR) and respiratory rate (RR) for each induction regimen. Mean values were only calculated when PR or RR were recorded for all four time periods (some measurements were not recorded accidentally or because of time constraints). For purposes of calculation, 60 breaths per minute were assigned to dogs that were noted to be panting.

The following table has nine columns.

Induction Regimen PR, RR (n,n)	Physical Examination		Pre-induction		Induction		Pre-procedure		
	PR	RR	PR	RR	PR	RR	PR	RR	

Propofol Only (98,90)	113	44	129	43		133	26	130	26
Propofol Acepromazine (41,41)	125	44	124	28		122	18	118	23
Propofol Oxymorphone (44,41)	111	42	114	60		111	31	104	30
Propofol Xylazine (40,40)	109	41	80	25		81	20	84	19
Propofol	116	39	111	37		122	31	116	34

Butorphanol
(20,20)

Propofol	114	39	97	25	105	24	94	27
Butorphanol/ acepromazine (20,20)								

PR:

Mean PR were variable depending on the premedicant. PR decreased in the xylazine and ace/butorphanol groups during the preinduction period. Oxymorphone, acepromazine, and butorphanol caused minimal changes in PR.

A transient increase in PR was seen after propofol induction when either butorphanol or ace/butorphanol were used for premedication. Following induction with propofol in the other premedication groups, minimal changes in PR were noted.

RR:

Premedicants during the preinduction period decreased RR in the ace, xylazine, and ace/butorphanol groups, caused minimal changes in the propofol only and butorphanol groups, and increased RR in the oxymorphone group.

On the whole, propofol induction caused RR to decrease in all groups; however, the decrease was minimal in the ace/butorphanol group.

Blood Pressure:

Measurements were taken at preinduction, induction, and preprocedure periods to determine the effect on BP of propofol alone or in conjunction with premedicants.

Systolic, diastolic, and mean BP were measured at one facility (MSU) in 22 dogs. The following table shows the mean values for the four test groups that were investigated at this facility. Butorphanol and ace/butorphanol were not investigated at this facility.

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The following table has eleven columns.

Induction Regimen	n	Pre-induction Mean			Induction Mean			Pre-procedure Mean					
		Sys	Dia	Mean	Sys	Dia	Mean	Sys	Dia	Mean			

Propofol Only	5	159	76	86		137	89	102		129	81	89	
Propofol Acepromazine	1	143	95	116		154	99	119		118	60	78	
Propofol Oxymorphone	13	146	89	106		118	60	78		107	55	73	
Propofol Xylazine	3	119	71	90		146	102	114		102	62	78	
Range Minimum	22		105	53	59		96	50	61		82	43	56
Range Maximum	22		184	119	140		178	120	134		145	99	117

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Systolic BP only was measured at two other sites (CSU & HEAC). The following table shows the mean systolic BP values for all the test groups evaluated at all three sites (MSU, CSU, HEAC):

Induction Regimen	n	Pre-induction Mean Systolic Blood Pressure	Induction Mean Systolic Blood Pressure	Pre-procedure Mean Systolic Blood Pressure
Propofol Only	7	148	142	128
Propofol Acepromazine	2	122	132	114
Propofol Oxymorphone	24	142	119	109
Propofol Xylazine	9	138	142	122
Propofol Butorphanol	2	120	117	120
Propofol Butorphanol/ acepromazine	5	102	107	102
Range Minimum	49	75	92	75
Range Maximum	49	200	201	190

BP results were variable depending on the premedicant. Prior to induction, BP increased with acepromazine and xylazine premedication, and decreased with propofol only or oxymorphone premedication. Systolic BP decreased for all regimens during the time period between induction and the start of the procedure.

Most of the mean BP in these tables are within acceptable clinical ranges. Systolic BP for a few dogs was outside the "normal" range (hypotensive or hypertensive). These dogs tolerated anesthesia without problems. The study raised no safety concerns regarding BP following the use of propofol for induction with and without premedicants.

Oxygen Supplementation:

Dogs (n = 123) that received only an induction dose of propofol or propofol maintenance anesthesia received oxygen supplementation at the discretion of the investigator. Of these dogs, 82 were not supplemented with oxygen for propofol induction or induction/maintenance. These dogs breathed room air for short procedures and recovered normally while breathing room air. One of these dogs experienced apnea that resolved without administration of oxygen.

Although 82 cases were completed without administration of supplemental oxygen, the procedures were short and uncomplicated in primarily healthy dogs. Twenty-five dogs received a single dose of propofol. Conclusions cannot be drawn concerning the safety of using propofol without available oxygen supplementation. Therefore, the label contains "boxed" warning information stating that the use of propofol without available supplemental oxygen and artificial ventilation has not been adequately evaluated and is not recommended.

Side Effects:

Apnea:

Induction apnea (within 10 minutes of induction) was the most common side effect of propofol administration (20%). The following table contains a comparison of cases of apnea by the various induction regimens.

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Incidence of induction (I) and maintenance (M) apneas
and duration of apnea (mean and range; min:sec)

Regimen N	Number of Apnea Observations (%)	Duration of Apnea Mean Range
Propofol Only* 141	28 I (20%)	3:42 0:14 - 18:00
Propofol / Acepromazine 47	5 I 1 M (13%)	11:17 1:13 - 17:53
Propofol / Oxymorphone** 48	16 I 1 M (35%)	8:56 1:17-27:00
Propofol / Xylazine** 41	5 I 2 M (17%)	4:14 0:31-12:45
Propofol / Butorphanol 24	2 I (8%)	9:40 7:41-11:39
Propofol / Butorphanol / Acepromazine 24	4 I (17%)	9:09 1:00-27:48
Total - 325	60 I 4 M (20%)	

* 2 end of apnea times not recorded

** 1 end of apnea time not recorded

The incidence of apnea and the mean duration of apnea varied by premedicant regimen. Dogs given propofol alone or with xylazine premedication, had mean durations of apnea of approximately 4 minutes. Dogs which received the remaining premedication regimens had mean durations of apnea of approximately 9 - 11 minutes. In addition to propofol's depression of the respiratory center, the opioid premedicants (oxymorphone, butorphanol) affect the response to the presence of CO₂, as does the administration of oxygen (depression of respiration) and assisted ventilation (CO₂ washout depresses respiration). This may

be the reason apnea was longer in duration for these premedicant treatment groups compared to propofol alone or with xylazine.

Propofol induction after oxymorphone premedication had the highest incidence of apnea (17/48; 35 %). Therefore, the total amount of propofol administered for induction after oxymorphone premedication was considered too high for some dogs. The induction dose for propofol should range from 2.2 mg/kg (1.0 mg/lb) to 3.3 mg/kg (1.5 mg/lb) to reduce the incidence of apnea, and this adjustment was made in the Induction Dosage Guidelines.

Two occurrences of apnea during maintenance with inhalant anesthesia were due to excess depth of anesthesia from high vaporizer settings and concurrent propofol incremental doses administered during inhalant anesthesia. The concurrent administration of propofol with a simultaneous increase in inhalant concentration is not recommended during maintenance anesthesia.

There were also two incidences of apnea following maintenance injections of propofol. Regardless of incidence or length, all apnea cases were managed with oxygen supplementation and assisted or controlled ventilation.

Side Effects Other Than Apnea:

1. Respiratory (n = 16; 4.9%, excluding apnea):

- reverse sneezing (n = 10)
- panting throughout procedure (n = 3)
- shallow, slow respirations throughout procedure (n = 1)
- non-productive cough during recovery (n = 1)
- brief, respiratory "rattle" during recovery (n = 1)

2. Neurological (n = 18; 5.5%):

- excitation during induction (n = 3)
- excitation during recovery (n = 4)
- excitation throughout procedure (n = 1)
- opisthotonus (n = 4)
- nystagmus (n = 2)
- head tilt, circling (n = 1)
- petit mal seizure or seizure-like activity (n = 2)
- excessive depression (n = 1)

3. Musculoskeletal (n = 35; 10.8%):

- paddling during recovery (n = 20)
- paddling during maintenance (n = 1)

- tremors during induction (n = 3)
- tremors during maintenance (n = 3)
- tenseness (n = 3)
- foreleg movement (n = 2)
- fasciculations (n = 1)
- shivering during recovery (n = 1)

4. Gastrointestinal (n = 14; 4.3%):

- emesis/retching during procedure (n = 2)
- emesis/retching during recovery (n = 8)
- salivation and/or drooling throughout procedure (n = 1)
- salivation and/or drooling throughout recovery (n = 2)
- defecation during recovery (n = 1)

5. Cardiovascular (n = 11; 3.4%):

- tachycardia during induction (n = 1)
- bradycardia (n = 8)
- cyanosis (n = 1)
- hypotension (n = 1)

6. Other (n = 24; 7.4%):

- slow recovery (n = 11)
- rubbing at face or nose during recovery (n = 5)
- vocalization during recovery (n = 2)
- extravascular pain (n = 3)
- intravascular pain (n = 1)
- chewing movement during intubation (n = 1)
- response to noise (n = 1)

Some of the anesthetic side effects are not unique to propofol. Some side effects noted during recoveries from propofol were also noted for recoveries from the inhalants with similar incidence (propofol : inhalant), e.g., paddling (10:10), opisthotonus (3:1), nystagmus (1:1), and vocalization (1:1). These recovery side effects following propofol induction with inhalant maintenance are assumed not to be due to propofol since the duration of inhalant anesthesia exceeded the 23 minute mean duration that propofol alone provided anesthetic effect (means of 7 minutes anesthesia for propofol induction and 16 minutes from end of anesthesia to standing).

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Side effects were, overall, transient and resolved on their own. Many anesthetic and physiological side effects noted during the field study were not unique to propofol but are also typically observed in any population receiving premedication to anesthesia and/or anesthesia regardless of the anesthetic agent.

One case of pain following intravascular injection was noted; three of 9 extravascular injections of propofol caused pain. Pain during propofol injection has been noted in other studies and in the literature.

One death (CVH, 7/20/95, #14622-B) occurred eight hours after anesthesia that was not attributed to anesthesia (propofol induction, halothane maintenance). The patient was an obese geriatric dog admitted for minor surgery (eyelid tumor, aural hematoma). The dog experienced a prolonged recovery, but died > five hours after recovery. Death was attributed to possible cardiac insufficiency by the pathologist.

Sighthounds:

During the course of the study eleven sight hounds (10 greyhounds and 1 Irish wolfhound) were anesthetized. These breeds have been reported to be more sensitive to anesthesia than other breeds.

Regimen	Number	Apnea
Propofol induction, isoflurane maintenance	9	0
Oxymorphone, propofol, halothane	1	1 (8'11")*
Butorphanol, propofol, halothane	1	0

*The recommended propofol dose for use with this premedicant has been reduced on the label from the dose used in the clinical trial.

Propofol was administered over 11 to 60 seconds. No side effects were noted except for one episode of apnea (propofol given over 60 seconds).

Anesthetic induction with propofol was satisfactory; however, all sighthounds were maintained with inhalant anesthetics. No conclusions can be drawn on the efficacy or safety of propofol as a maintenance anesthetic in sighthounds or on anesthetic recovery from propofol. However, in the literature, propofol anesthesia has been associated with longer recovery periods in sighthounds (see reference Robertson, et.al., 1992).

II. THE EFFICACY OF RAPINOVET IN CATS WAS DEMONSTRATED IN FIVE STUDIES:

- A. 1 - PROPOFOL DOSE DETERMINATION STUDY FOR INDUCTION OF ANESTHESIA
- B. 2 - PROPOFOL DOSE DETERMINATION STUDY FOR INDUCTION OF ANESTHESIA
- C. PROPOFOL DOSE DETERMINATION STUDY FOR MAINTENANCE OF ANESTHESIA
- D. COMPATIBILITY STUDY OF PROPOFOL IN CATS WHEN USED WITH PREANESTHETICS AND INHALANT ANESTHETICS
- E. CLINICAL TRIAL UNDER FIELD CONDITIONS WITH PROPOFOL IN CATS

A-C. DOSE DETERMINATION STUDIES

The objective of these three studies was to determine effective induction and maintenance doses of propofol, and to measure the mean duration of anesthesia in cats. The formulation for the injectable anesthetic was the same as the market formulation. Placebo controls were not used due to the nature of the drug being investigated (anesthetic). Each cat served as its own control in that it was either anesthetized or not anesthetized as determined by reflex response to tail clamp, purposeful movements, or other clinical observations. The ability to intubate the cat was an important consideration for determining the depth of anesthesia achieved. The duration of administration of the dose was recorded. The duration of anesthesia was measured from induction (loss of tail clamp reflex) to the end of anesthesia (when the tail clamp reflex returned). The duration of the recovery period was measured from the end of anesthesia through head lift, sternal recumbency, until full standing. The three studies were conducted by:

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A. INDUCTION DOSE TITRATION STUDY (1)

Sawyer and Salsbury (1995a) conducted an induction dose titration study in 30 cats. The cats were divided into 3 groups of 5 males and 5 females each. Propofol was administered as a single dose of

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3.3, 6.6 or 9.9 mg/kg, delivered during periods of approximately 30, 60 or 90 seconds, respectively (dose rate approximately 6.6 mg/kg/min). Observations included: induction time, duration of anesthesia, and recovery time, all as defined above; respiratory rate; pulse rate; systolic, diastolic, and mean arterial blood pressure; oxygen saturation; and adverse reactions.

Only one of ten cats given 3.3 mg/kg was anesthetized. The anesthesia is that one cat lasted 4:45 (min:sec) and did not allow intubation of the cat. Recovery from anesthesia was essentially instantaneous.

Eight of ten cats given 6.6 mg/kg of propofol were anesthetized (mean of 4:30, range 1:30 - 7:21), but only two of the eight could be intubated. Total recovery was achieved in a mean of 12:43 (range 5:01 - 24:36).

All cats given 9.9 mg/kg of propofol were anesthetized (mean of 11:31, range 7:05 - 18:51), but only six of the ten could be intubated. Recovery took a mean of 20:20 (range 10:18 - 37:33).

None of the anesthetized cats exhibited apnea. Respiration rates decreased following induction, while pulse rates were increased. Systolic, diastolic, and mean blood pressures were generally lower during anesthesia. Oxygen hemoglobin saturation was not measured prior to induction of anesthesia; levels were 83 - 90 % at 2 minutes post-induction. Oxygen supplementation was provided to intubated cats whenever the value was below 90 %, and subsequent readings were usually (16 / 19) above 90 %.

Adverse reactions were observed in two cats at 9.9 mg/kg: nystagmus and excitement during recovery in one cat and opisthotonos during recovery in the other. These findings resolved normally by the end of recovery.

Anesthesia lasting at least 7 minutes was achieved in all cats at 9.9 mg/kg, the highest dose tested. However, this level of propofol was not a sufficient induction dose for procedures requiring intubation in four of the ten cats tested.

B. INDUCTION DOSE TITRATION STUDY (2)

Sawyer and Salsbury (1995b) conducted a second induction dose titration study in 30 cats divided into 3 groups of 5 males and 5 females each. Propofol was administered as a single dose of 8.8, 11.0 or 13.2 mg/kg, delivered over approximately 30, 60, or 90 seconds, respectively. Observations included: induction time, duration of anesthesia, and recovery time, all as defined above; respiratory rate; pulse rate; systolic, diastolic, and mean arterial blood pressure; oxygen saturation; and adverse reactions.

All 30 cats were anesthetized with propofol. At 8.8 mg/kg, anesthesia lasted for an average of 10 minutes:57 seconds (range 7:33 - 15:58), while recovery was achieved in an average of 25:16 (range 6:55 - 44:52). Four of the ten cats could not be intubated.

Cats given 11.0 mg/kg of propofol were anesthetized for a mean of 15:11 (range 7:40 - 36:00) and recovery took a mean of 26:43 (range 11:44 - 53:09). Four of the ten cats could not be intubated.

For those animals which received 13.2 mg/kg of propofol, anesthesia lasted 17:35 (range 12:13 - 29:20) and recovery was achieved in 26:31 (range 20:49 - 36:28). All ten cats given 13.2 mg/kg of propofol were intubated.

None of the anesthetized cats exhibited apnea. Respiration rates decreased following induction, while pulse rates were not markedly affected. Systolic, diastolic, and mean blood pressures were generally lower during anesthesia compared with pre-induction readings. Oxygen hemoglobin saturation was not measured prior to induction of anesthesia; levels were 71 - 94 % at 2 minutes post-induction. Oxygen supplementation was provided to any intubated animal whenever oxygen hemoglobin saturation values were below 90 % (N = 25), and post-supplement readings were usually (50 / 56) above 90 %.

Adverse reactions were noted in 9 cats. These reactions were minor (excitement, opisthotonos, pawing at the face, sneezing, gagging) and resolved by the end of the recovery period (N = 8) or shortly thereafter (N = 1).

The lowest dose tested, 8.8 mg/kg of propofol, was a sufficient induction dose for short procedures (< 7 minutes) which do not require intubation. The highest dose tested, 13.2 mg/kg of propofol, was a sufficient induction dose for procedures which require intubation. The duration of anesthesia increased as the dose increased, but recovery times were unchanged. Based upon this study and the previous one (Sawyer and Salsbury, 1995a), the range for the propofol induction dose was established as 8.8 to 13.2 mg/kg, delivered over approximately 60 - 90 seconds. Selection of a dose within the range is dependent upon the depth (and duration) of anesthesia desired, or more commonly, will be the end result of dosing to effect.

C. MAINTENANCE DOSE TITRATION STUDY

Sawyer and Salsbury (1995c) conducted a maintenance dose titration study in 30 cats. The cats were divided into 3 groups of 5 males and 5 females each. Propofol was administered to all cats as a single induction dose at 13.2 mg/kg, delivered during a period of approximately 60 seconds. All cats were intubated, which was maintained throughout the time of anesthesia. When each animal started to recover from anesthesia (by reacting to tail clamping or by other signs), a maintenance dose of propofol was administered. This procedure was repeated as necessary until the cat had been anesthetized for a total of 30 minutes. Maintenance doses selected were 1.1, 2.2 and 4.4 mg/kg, given over 60 seconds (1.1, 2.2 or 4.4 mg/kg/min, respectively). Observations included: induction time, duration of anesthesia, and recovery time, all as defined above; number of doses and dose volume; respiratory rate; pulse rate; mean arterial blood pressure; oxygen saturation; rectal temperatures; and adverse reactions.

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All dose levels of propofol maintained anesthesia in all cats. The average number of 1.1 mg/kg maintenance doses required to achieve 30 minutes of anesthesia was 3.9 (range 2 - 7), and the average time from the end of anesthesia to full standing recovery was 31:57 (range 15:49 - 51:35).

The level of 2.2 mg/kg (N = 9; one cat did not receive any maintenance doses) required an average of 2.4 doses (range 1 - 6), and the average time from the end of anesthesia to full standing recovery was 31:03 (range 8:45 - 64:25).

The cats receiving 4.4 mg/kg needed only 1.6 doses of propofol (range 1 - 2), which was less than that required at 1.1 mg/kg ($P < 0.05$). The average time from the end of anesthesia to full standing recovery was 30:09 (range 17:48 - 56:04).

Four of the anesthetized cats exhibited apnea with a total of five episodes. One occurred shortly after the induction dose was given, two shortly after maintenance doses were administered (1.1 and 2.2 mg/kg), and two during anesthesia (one before any maintenance dose and one 4 minutes after 2.2 mg/kg).

Respiration rates decreased immediately following induction and remained low throughout anesthesia. Pulse rates decreased slowly through 10 minutes post-induction, then remained stable throughout anesthesia. Systolic, diastolic, and mean blood pressures decreased through 5 minutes post-induction, then remained stable during the remainder of anesthesia. Oxygen hemoglobin saturation was not measured prior to induction of anesthesia; levels were 77 - 97 % at 2 minutes post-induction. Oxygen supplementation was provided to any animal whenever oxygen hemoglobin saturation values were below 90 % (N = 19 animals, 24 timepoints), and the next values were usually (20/23, 1 not recorded) above 90 %. Rectal temperatures declined steadily throughout anesthesia, with a total drop of 3 - 4 °F.

Some adverse reactions were noted during recovery in 15 cats (3 at 1.1 mg/kg, 5 at 2.2 mg/kg, and 7 at 4.4 mg/kg). These reactions included excitement, opisthotonos, paddling, pawing at the face, sneezing, gagging, and mild tremors. All of the reactions resolved by the end of the recovery period.

Based on these results, anesthesia can be maintained in unpremedicated cats with propofol in the range of 1.1 - 4.4 mg/kg, delivered at an even rate over a period of approximately 60 seconds. The duration of anesthesia from a single maintenance dose can be regulated by selection of the dose level (lower doses for shorter duration; higher doses for longer duration). Recovery time may be slightly longer (~ 5 minutes under these study conditions) for cats which receive multiple doses of propofol compared with those receiving only one dose.

D. COMPATIBILITY STUDY

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The objective of this study was to determine the pharmacophysiological responses of cats when propofol was used in conjunction with pre-anesthetics, or as an induction agent prior to inhalant anesthetics. The formulation for the injectable anesthetic was the same as the market formulation. Placebo controls were not used due to the nature of the drug being investigated (anesthetic). Each cat served as its own control in that it was either anesthetized or not anesthetized as determined by reflex response to tail clamp, purposeful movements, ability to intubate, or other clinical observations. The study was conducted by:

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1) Pre-anesthetics Plus Propofol For Induction and Maintenance Of Anesthesia:

Sawyer and Campbell (1997) determined the compatibility of propofol when used in combination with various pre-anesthetics. The study design utilized 10 groups of cats (N = 3 males and 3 females per group; cats were used more than once). Products or product combinations tested included atropine, glycopyrrolate, acepromazine, midazolam, ketamine, xylazine, oxymorphone, butorphanol, acepromazine plus oxymorphone, and acepromazine plus butorphanol. The preanesthetic drugs were given approximately 15 minutes prior to induction of anesthesia. Intramuscular doses of the preanesthetic agents are shown in the following table.

Intramuscular Doses of Preanesthetic Drugs

Group	Preanesthetic	Dose mg/kg	Group	Preanesthetic	Dose mg/kg
1	acepromazine	0.1	6	acepromazine	0.1
				oxymorphone	0.05
2	butorphanol	0.1	7	atropine	0.02
3	ketamine	8.0	8	glycopyrrolate	0.01
4	oxymorphone	0.05	9	midazolam*	0.2
5	acepromazine	0.1	10	xylazine	0.4

butorphanol 0.1

*The safety of general anesthesia with propofol when used in conjunction with midazolam premedication was evaluated. However, midazolam is not approved as a preanesthetic in cats.

The induction dose of propofol (13.2 mg/kg) was placed in a syringe, and the animal was dosed to effect (target administration 60 seconds). If the cat reached a level of anesthesia adequate for intubation before completion of the calculated dose, dosing was stopped and the amount of propofol used was recorded. If the level of anesthesia was not sufficient for intubation, additional propofol was administered at the same rate (13.2 mg/kg/min) until anesthesia was adequate, and the total dose recorded. After induction, all cats were intubated, given oxygen, and maintained for at least 30 minutes. Anesthesia was maintained by intermittent doses of propofol, calculated at 2.2 mg/kg delivered over 60 seconds, with the total actual dose and time recorded. Observations included: volume of propofol used at each injection and number of injections; induction time, maintenance dose time(s), duration of anesthesia, and recovery time, all as defined previously; respiratory rate; pulse rate; mean arterial blood pressure; oxygen saturation; rectal temperatures; and adverse reactions.

If one or more of the six cats per group in Groups 1-10 required the full 13.2 mg/kg calculated induction dose of propofol, the pre-anesthetic drug was judged to have had no effect on the upper end of the dose range of propofol required for intubation. If the mean induction dose was not markedly reduced, requiring less than 8.8 mg/kg, the preanesthetic drug was judged to have had no effect on the lower end of the dose range of propofol required for anesthesia induction. The number of repeat injections required to maintain anesthesia was indicative of the duration of anesthesia from both the induction dose and the maintenance doses.

Physiological response summary for all 12 groups (includes 2 inhalant maintenance groups):

The mean respiration rate prior to administration of preanesthetics was 68.6 breaths / minute (range 36 - 120; N = 72). Pulse rates had a mean value of 151.8 beats / minute (range 50 - 242; N = 69). The mean systolic arterial blood pressure was 107.0 mm Hg (range 36 - 182; N = 69). The mean diastolic arterial pressure was 72.7 mm Hg (range 29 - 151; N = 69). The mean arterial pressure was 84.3 mm Hg (range 34 - 156; N = 69).

The following table shows the dose and time interval data for all premedicated groups treated with propofol maintenance. The elapsed time between preanesthetic administration and induction ranged from 15 to 35 minutes. This range in time may have contributed to variations in the preanesthetics' dose-sparing effects on the induction dose of propofol .

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preanesthetic	induction dose avg (range)	number maint. doses	anesthesia duration avg (min:sec)	recovery time avg (min:sec)
atropine	12.7 (11.0-13.4)	2-3	40:24	28:22
glycopyrrolate	11.2 (8.9-13.3)	2-6	40:08	23:25
acepromazine	11.4 (9.6-13.2)	1-2	46:06	26:50
midazolam	8.8 (7.7-9.9)	1-3	40:37	43:04
ketamine	8.2 (7.7-9.5)	1-2	40:54	34:23
xylazine	9.2 (7.1-12.0)	0-1	58:29*	27:20
oxymorphone	11.3 (9.2-13.2)	1-3	51:16	21:49
butorphanol	12.2 (7.8-16.5)	0-3	42:59	33:17
ace + oxymorphone	8.6 (7.7-9.9)	0-1	43:54 ⁺	21:05
ace + butorphanol	10.4 (8.4-12.1)	0-2	45:10	26:10

* only one cat required maintenance dosing

⁺ three cats required maintenance dosing

Respiration and heart rate parameters are presented in the following table. Ranges are for all cats in the specified group over the entire duration of anesthesia. Averages and ranges are given for the pretreatment observations for all cats in the study.

GROUP	RR breaths/min (avg) range	HR beats/minute (avg) range	systolic BP mm Hg (avg) range	diastolic BP mm Hg (avg) range	mean arterial BP (avg) range
pretreatment	36-120	50-242	36-182	29-151	34-156
atropine	3-20	129-228	51-114	30-73	40-81
glycopyrrolate	3-28	108-200	34-116	20-85	25-90
acepromazine	9-24	45-190	68-122	30-82	38-106
midazolam	3-28	87-186	62-122	29-74	37-94
ketamine	3*-24	60-216	35-123	24-92	29-110
xylazine	8-36	0 ⁺ -142	0 ⁺ -138	0 ⁺ -96	0 ⁺ -117
oxymorphone	4-24	64-177	47-94	25-61	32-77
butorphanol	5-24	64-160	60-116	25-80	33-92
ace+oxymorphone	3-32	86-173	53-136	24-96	31-116
ace+butorphanol	8-24	88-166	68-101	29-53	37-73

* 3 cats developed apnea (4 episodes) and required manual breathing assistance for up to 35 min.

+ next lowest observed values were: pulse 85, systolic 37, diastolic 26, mean arterial BP 16. Instrumentation frequently could not be measure BP and HR in the xylazine preanesthetic group, due to peripheral vasoconstriction caused by this alpha-2-agonist.

Oxygen hemoglobin saturation ranged from 66-98% at 2 minutes post-induction across all groups. Oxygen supplementation was provided to all cats during maintenance anesthesia, and the oxygen

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hemoglobin saturation values were nearly always above 90%. Rectal temperatures dropped from 3-5° F across all groups.

The following side effects were reported:

Adverse reactions by treatment group, numbers of incidences recorded.

GROUP	Reactions, numbers of incidences
atropine	pawing face, 2
glycopyrrolate	pawing face, 5
acepromazine	pawing face, 2; shaking 1
midazolam	pawing face, 1; paddling, 2; opisthotonus, 1; excitement, 1
ketamine*	apnea, 4 episodes in 3 cats
xylazine	muscle spasms, 1
oxymorphone	laryngospasms, 2; kicking (recovery), 2; excitement, 2; head tilt, circling, 1
butorphanol	muscle spasms, 3; pawing faces, 2; opisthonos, 1
ace+oxymorphone	tracheal spasms, 1; cyanosis, 1
ace+butorphanol	cyanosis, 1; licking, 1; excitement (recovery), 2

*** Based on the high incidence of apnea following ketamine as a preanesthetic, the routine use of this combination is not recommended.**

Overall Summary

These investigations showed that the use of propofol for induction of anesthesia, utilizing common preanesthetic agents, is safe and effective. The required dose of propofol may be reduced following some premedicants, the duration of anesthesia may be affected (either shorter or longer), and recovery time may also be affected (again, either shorter or longer).

Physiological responses to propofol anesthesia were relatively consistent (for example, decreased respiration and pulse rates, decreased blood pressure, decreased body temperature) and require monitoring. Apnea and respiratory depression were common following the use of ketamine and propofol, and thus ketamine is not recommended as a preanesthetic prior to propofol administration.

Minor adverse reactions were noted either at the beginning of anesthesia or during recovery, but these all resolved spontaneously and do not indicate a specific problem with any preanesthetic regimen.

2) Propofol For Induction Plus Inhalants For Maintenance of Anesthesia:

Dose and time interval data for groups treated with inhalant maintenance anesthesia.

GROUP	propofol induction dose avg (range)	anesthesia duration avg (min:sec)	recovery time avg (min:sec)

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halothane	11.7 (8.6-13.2)	41:46	31:28
isoflurane	11.2 (8.4-13.3)	42:37	21:24

Respiration and heart rate parameters for groups treated with inhalant maintenance anesthesia. Ranges are for all cats in the specified group over the entire duration of anesthesia.

GROUP	RR breaths/min range	HR beats/minute range	systolic BP mm Hg range	diastolic BP mm Hg range	mean arterial BP range
halothane	6-24	96-177	61-126	29-70	39-105
isoflurane	4-21	100-210	64-119	26-72	34-89

Oxygen hemoglobin saturation ranged from 89-97% at 2 minutes post-induction. Oxygen supplementation was provided to all cats during maintenance anesthesia, and all but 4 of the values of oxygen hemoglobin saturation after 2 minutes were above 90%. Rectal temperatures dropped from 3-4° F.

The following side effects were reported.

Side effects by treatment group, numbers of incidences recorded.

GROUP	Reactions, number of incidences
halothane	salivation, 1; pawing face, 3; reverse sneezing, 1
isoflurane	pawing face, 4; reverse sneezing, 1

Based on these two groups of cats, propofol is both effective and safe for induction of anesthesia which will be maintained by an inhalant.

E. CLINICAL FIELD TRIAL:

There were three major efficacy objectives for this trial. First, to determine the clinical effectiveness of propofol when administered solely as an intravenous anesthetic agent in cats. Second, to determine the clinical effectiveness when propofol was administered in conjunction with routinely used pre-anesthetic agents in cats. Third, to determine the clinical effectiveness of propofol in cats when administered solely for induction of anesthesia with subsequent maintenance by inhalant anesthetics. The study was conducted by:

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Peterson (1997) conducted a clinical field study at 4 locations (8 investigators) with 212 cases presented for surgery and / or other procedures requiring anesthesia. The study population was divided into three major treatment classifications: 1) propofol as the sole anesthetic, either as a single injection for induction, or with repeated administrations to maintain anesthesia; 2) propofol induction in conjunction with various pre-anesthetics, maintained, if necessary, with propofol or inhalant anesthetics; and 3) propofol only induction of anesthesia with subsequent maintenance by inhalant anesthetics, either halothane or isoflurane.

The treatment regimen was determined by the length of the procedure, type of surgery, occasionally by temperament of the cat, and by test facility capability. Pregnant cats were excluded from the study. Data recorded included information on the patients and procedures, anesthetic performance (ease of induction, duration and nature of anesthesia, duration and nature of recovery, overall satisfaction), physiological parameters (respiration rate, pulse rate, blood pressure), and adverse reactions (see safety section, below).

1) PATIENTS AND PROCEDURES:

Description

A varied number of breeds and crossbreeds were represented. The cats ranged in age from 2 months to 16 years and in weight from 0.5 to 9.1 kilograms. The study included 103 males (intact and castrated), and 104 females (intact and spayed) for a total of 207 animals. There were instances when the same cat was anesthetized more than one time during the study, and these were considered a separate case each time (212 total cases).

Procedures

The most common procedures for which cats were admitted to the study were castrations, ovariectomies, dental cleanings, tumor removals, and X-rays. Multiple procedures were completed during anesthesia in some cats.

Concomitant Treatments

Concomitant therapies were not widely administered to test animals. The compounds reported were aminophylline, amoxicillin trihydrate + clavulanate potassium, diazepam, enrofloxacin, imidacloprid, metoclopramide, pancuronium bromide, praziquantel, and ranitidine hydrochloride.

Health Status

A summary of the number of cats per health status based on classification by the American Society of Anesthesiologists (ASA) is shown in the following table.

ASA Health Status

	ASA	ASA	ASA	
Preanesthetic	Class	Class	Class	N
	1	2	3	
None	37	5	2	44
Acepromazine	41	9	2	52
Butorphanol	38	13	3	54
Xylazine	53	8	1	62
Total	169	35	8	212

Eighty percent (169 / 212) of the cats were classified as ASA Class 1, healthy without any apparent underlying condition. A variety of reasons were listed for the 35 (16%) ASA Class 2 animals: geriatric (20) +/- mild weight loss, severe stomatitis, chronic renal disease, electrolyte imbalance, obesity, FIV positive, hyperthyroid, or squamous cell carcinoma; pregnancy (2); obesity (2); fibrosarcoma (1); mediastinal mass (1); wheezing (1); mild cough with unilateral serous discharge (1); pulmonary disease (1); hypertrophic cardiomyopathy (1); hit by car (1); laryngeal mass (1); fracture (1); stray, unknown history (1); and hepatic lipidosis (1). Reasons for the 8 (4%) ASA Class 3 cats were: geriatric with other underlying conditions (2); obesity with other underlying conditions (2); heart murmur, renal failure (1); cholangiohepatitis (1); hepatic fibrosis (1); and renal disease, hyperthyroid (1).

Study Design

The induction and maintenance dosages recommended in the protocol for the premedicants (acepromazine, butorphanol, xylazine), propofol, and the inhalants (halothane, isoflurane) were described. Because the label doses of the premedicants are for sole usage of the products as sedatives or tranquilizers, the doses recommended for premedication are usually lower than labeled amounts (see Thurman et al., 1996). The use of the anticholinergic atropine was at the discretion of the investigators, and was administered prior to propofol induction in 105 cases (49 %).

Protocol Recommended Induction And Maintenance Dosages (mg/kg)

For Propofol, Acepromazine, Butorphanol, Xylazine, Halothane, And Isoflurane

Preanesthetic Agent, Dose, and Route	Propofol*	Propofol*	Halothane**	Isoflurane**
	Induction	Maintenance	Maintenance	Maintenance
None	8.8 - 13.2	1.1 - 4.4	0.5 - 1.8 %	0.6 - 2.0 %
	mg/kg	mg/kg	or as required	or as required
Acepromazine	8.8 - 13.2	1.1 - 4.4	0.5 - 1.8 %	0.6 - 2.0 %
0.1 mg/kg	mg/kg	mg/kg	or as required	or as required
IM or SC				
Butorphanol	8.8 - 13.2	1.1 - 4.4	0.5 - 1.8 %	0.6 - 2.0 %
0.2 mg/kg	mg/kg	mg/kg	or as required	or as required
SC				
Xylazine	6.6 - 9.9	1.1 - 2.2	0.5 - 1.8 %	0.6 - 2.0 %
0.5 mg/kg	mg/kg	mg/kg	or as required	or as required
IM or SC				

* Propofol was administered intravenously

** Initial vaporizer settings were 2.5 % or as required.

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The table summarizes agent, route of delivery, mean dosage actually used (and range), mean time interval to propofol administration (and range), and premedication effect.

Preanesthetic Agents, Incidence (N), Route of Administration, Mean and Range of Dosage Delivered (mg/kg), Mean and Range of Time Interval Between Premedication and Propofol Induction (minutes), and Effect of Agent

Preanesthetic	Route		Dose (mg/kg)	Interval to Propofol Induction (min)	Effect of Agent	N
	IM	SC	Mean + Range	Mean + Range*		
N	N	N	0.1	59	Mild	40
					Moderate	12
52	14	38	0.04 - 0.20	1 - 283		
Butorphanol			0.2	57	Mild	43
					Moderate	10
54		54	0.09 - 0.79	11 - 324	Other	1
Xylazine			0.8	55	Mild	19
					Moderate	33
62	28	34	0.29 - 2.05	20 - 169	Profound	10

* The wide range of time intervals between premedication and propofol induction administrations probably influenced the dosage of propofol and duration of activity.

2) ANESTHETIC PERFORMANCE:

Induction of Anesthesia

Qualitative scores for ease of induction using propofol alone or with premedications were mostly categorized as excellent or good (propofol only, 95.4 %; acepromazine, 100 %; butorphanol, 96.2 %; xylazine 96.7 %).

The mean induction dose for 44 cats given propofol only (no premedication) was 10.0 mg/kg (range 2.6 - 15.6 mg/kg). The 52 cats given acepromazine were subsequently administered a mean induction dose of 8.7 mg/kg of propofol (range 2.0 - 13.0 mg/kg). The mean induction dose for 52

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(2 cases excluded due to stopwatch errors) cats given butorphanol was 9.1 mg/kg of propofol (range 2.2 - 13.9 mg/kg). The 60 (2 cases excluded due to stopwatch errors) cats given xylazine resulted in a mean induction dose of 6.7 mg/kg propofol (range 1.5 - 11.0 mg/kg).

Based upon this data and that from previous pre-clinical and clinical studies, dose ranges have been established for propofol induction, either alone or with various premedications (see the Induction Dosage Guidelines table in the package insert).

Quality and Duration of Anesthesia (Propofol; no Inhalants)

Anesthetic effectiveness scores of excellent or good for cases maintained with propofol were: propofol only, 100 %; acepromazine, 95 %; butorphanol, 94 %; and xylazine 90 %. These scores indicated that the regimens provided effective anesthesia for the procedures involved. With propofol, signs of arousal can develop rapidly; maintaining surgical depth of anesthesia and avoiding the first plane of arousal requires close attention.

There was some variability in the length of time an induction dose or an incremental dose of propofol provided anesthesia, depending upon the preanesthetic regimen.

Mean Anesthesia Intervals (min:sec) And Doses Of Propofol (mg/kg)

For Induction Doses, Maintenance Doses, And All Doses (Maintenance and Induction)

Preanesthetic	Induction Duration (min:sec) Dose (mg/kg) Number of cats	Maintenance Duration (min:sec) Dose (mg/kg) N	Duration for All Intervals (min:sec) (Maintenance + Induction N
None	6:32	7:05	6:51
	9.2	2.9	
	18	24	42
Acepromazine	8:29	6:10	7:13
	8.8	1.9	
	20	24	44
Butorphanol	9:00	11:12	10:29
	5.9	1.9	
	21	43	64
Xylazine	7:46	5:23	6:07
	10.3	1.6	
	16	36	52

Quality and Duration of Anesthesia (Propofol [+/- Premeds] plus Inhalants)

Cats were maintained with either isoflurane or halothane by changing vaporizer settings as necessary. Anesthetic effectiveness scores of excellent or good for cases where anesthesia was induced with propofol and then maintained by inhalants were: no premedication, 100 %; acepromazine, 98 %; butorphanol, 98 %; and xylazine 92 % (one case not recorded). These scores indicated that all of the regimens provided effective anesthesia for the procedures involved.

As expected, the cases which were maintained with inhalants involved longer periods of anesthesia than those which received no maintenance anesthesia or were maintained with propofol. Mean duration of anesthesia was 56:46 (range 8:24 - 164:04; N = 64) for the halothane maintenance group, and 51:58 (range 8:08 - 170:44; N = 73) for the isoflurane maintenance group.

Recovery

Recoveries scored as excellent and good were comparable for cats treated with propofol (96 %), propofol plus halothane (95 %), or propofol plus isoflurane (90 %).

The mean time from end of anesthesia to standing for cats that received only the induction dose of propofol (all regimens, N = 37) was 25:04. The mean time from end of anesthesia to standing for cats that received the induction dose and incremental dose(s) of propofol (all regimens, N = 36) was 34:18. This indicated that the effects of propofol on recovery were slightly cumulative when incremental maintenance doses of propofol were administered.

Means and ranges of elapsed times from the end of anesthesia to head lift, sternal recumbency, and standing, and recovery scores, are shown for cats which received no premedication.

Means And Ranges For Time (min:sec) From End Of Anesthesia To Head Lift, Sternal And Standing, And Recovery Scores* - No Premedication Administered

Maintenance	<u>Head Lift</u>	<u>Sternal</u>	<u>Standing</u>	Recovery
Regimen	Mean	Mean	Mean	Scores *
	Range	Range	Range	E G F P
None or propofol	16:22	21:48	28:23	17 2
	0:44 - 49:36	2:20 - 52:57	9:29 - 61:36	NR = 1
Halothane	16:16	19:54	26:22	14 3
	1:17 - 55:26	1:54 - 58:10	2:23 - 62:00	
Isoflurane	10:26	16:50	26:32	12 2 1
	0:00 - 35:42	1:20 - 37:26	5:52 - 53:20	

* Excellent (E), Good (G), Fair (F), Poor (P), Not Recorded (NR)

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Means and ranges of elapsed times from the end of anesthesia to head lift, sternal recumbency, and standing, and recovery scores, are shown for cats which received various premedications.

Means And Ranges For Time (min:sec) From End Of Anesthesia To Head Lift, Sternal And Standing, And Recovery Scores* - Premedications Administered

Preanesthetic and Maintenance Regimen	<u>Head Lift</u> Mean Range	<u>Sternal</u> Mean Range	<u>Standing</u> Mean Range	Recovery Scores *
				E G F P
Acepromazine	16:22	21:48	28:23	17 2
None Or Propofol	0:44 - 49:36	2:20 - 52:57	9:29 - 61:36	NR = 1
Acepromazine	16:16	19:54	26:22	14 3
Halothane	1:17 - 55:26	1:54 - 58:10	2:23 - 62:00	
Acepromazine	10:26	16:50	26:32	12 2 1
Isoflurane	5:42	1:20 - 37:26	5:52 - 53:20	
Butorphanol	17:53	24:32	28:19	10 4 1
None Or Propofol	0:38 - 58:14	1:46 - 77:15	10:21 - 81:56	NR = 1
Butorphanol	8:24	10:18	22:31	11 3 1 1
Halothane	1:30 - 22:18	3:36 - 23:16	7:06 - 53:20	
Butorphanol	8:55	15:21	23:51	14 7 1
Isoflurane	0:52 - 34:04	1:42 - 45:58	4:51 - 67:04	
Xylazine	18:49	24:57	34:39	16 4
None Or Propofol	0:00 - 64:31	0:29 - 86:40	3:35 - 108:20	NR = 1
Xylazine	13:00	15:58	28:29	10 7 1
Halothane	0:00 - 56:30	0:24 - 88:30	10:05 - 88:30	NR = 2
Xylazine	10:41	28:04	35:52	14 3 4
Isoflurane	0:00 - 31:49	1:26 - 315:00	2:00 - 315:00	

* Excellent (E), Good (G), Fair (F), Poor (P), Not Recorded (NR)

3) OXYGEN SUPPLEMENTATION:

All cats maintained with inhalants (137) had oxygen supplementation provided during the procedure. For the regimens requiring either no maintenance anesthetic (the induction dose of propofol was all the cat received) or propofol maintenance, oxygen supplementation was at the discretion of the investigator. Eighty-five percent (64 / 75) opted not to supplement with oxygen for short procedures, allowing cats to breathe room air throughout the procedure. Three cases did not have this information recorded. One of the 75 cats became apneic and was supplemented with oxygen, an accepted veterinary anesthetic practice for treatment of apnea. The apnea lasted for 3 minutes and 35 seconds. Seven additional cats were supplemented with oxygen even though apnea did not occur.

Although 64 cases were completed without administration of supplemental oxygen, the procedures were short and uncomplicated in primarily healthy cats. Thirty-seven cats received a single dose of propofol. Conclusions cannot be drawn concerning the safety of using propofol without available oxygen supplementation. Therefore, the label contains “boxed” warning information stating that the use of propofol without available supplemental oxygen and artificial ventilation has not been adequately investigated and is not recommended.

4) **PHYSIOLOGICAL PARAMETERS:**

Pulse Rates

Pulse rates were obtained at all four specified timepoints (physical examination, pre-induction, post-induction, and pre-procedure) for 188 cases. Pulse rates were increased by acepromazine and decreased by xylazine, as indicated by the pre-induction values. Pulse rates decreased following induction of anesthesia with propofol in pretreated animals, and decreased further in cats which received only propofol or propofol plus either butorphanol or xylazine.

Respiration Rates

Respiratory rates were obtained at the four specified timepoints for 196 cases. Respiration rates were decreased slightly by pre-treatment with xylazine. A substantial reduction in respiratory rate was seen immediately after propofol induction in all four test groups, with no further changes prior to initiation of the diagnostic or surgical procedure.

Mean Pulse Rates (PR; Beats/Minute) and Respiratory Rates (RR; Breaths/Minute)

Preanesthetic (N for PR, RR)	Physical Examination		Pre-Induction		Induction		Pre-Procedure	
	PR	RR	PR	RR	PR	RR	PR	RR
None (38, 43)	184	52	178	48	179	32	170	32
Acepromazine (44, 46)	191	49	210	50	179	32	179	31
Butorphanol (50, 54)	193	48	190	46	172	29	163	29
Xylazine (56, 53)	183	47	162	40	146	28	140	28

Blood Pressures

Systolic, diastolic, and mean blood pressures were measured at one test facility (University of Illinois; N = 13). Systolic blood pressures only were measured at another site (Colorado State University; N = 7). Combined systolic blood pressures for both sites are shown in (N = 20). Values were included in the following tables only if they were recorded at pre-induction, induction, and pre-procedure times for the same cat (recordings at physical examination were generally not done).

Results for diastolic and mean blood pressure were variable depending on the premedicant. The small number of cases for some treatments (for example, butorphanol and xylazine) make it difficult to extrapolate to the general population. For systolic blood pressure, where the group numbers were more consistent but still small, the data suggest that induction of anesthesia with propofol will decrease blood pressure except for cats pretreated with xylazine, where little or no change was observed.

Systolic (Sys), Diastolic (Dia), and Mean Blood Pressure (mm Hg)
[Data from University of Illinois]

Preanesthetic	N	Pre-Induction			Induction			Pre-Procedure		
		Sys	Dia	Mean	Sys	Dia	Mean	Sys	Dia	Mean
None	4	111	72	90	103	50	75	84	37	55
Acepromazine	6	95	63	72	77	46	56	76	37	53
Butorphanol	1	89	67	73	60	35	45	55	34	44

Xylazine 2 116 78 96 137 95 120 143 91 114

Systolic Blood Pressure (mm Hg)

[Pooled Data from University of Illinois and Colorado State University]

Preanesthetic	N	Pre-Induction	Induction	Pre-Procedure
None	5	110	101	86
Acepromazine	6	95	77	76
Butorphanol	4	101	74	82
Xylazine	5	110	115	111

5. TARGET ANIMAL SAFETY:

II. THE SAFETY OF PROPOFOL IN DOGS WAS EVALUATED IN THREE PIVOTAL STUDIES:

- A. ACUTE TOXICITY STUDIES IN BEAGLES BY INTRAVENOUS (IV) ADMINISTRATION.
- B. THIRTY DAY IV TOXICITY STUDY IN DOGS.
- C. IV TOLERANCE STUDY IN DOGS.

A. ACUTE TOXICITY STUDIES IN BEAGLES BY IV ADMINISTRATION:

Study Directors:

Dr. I. D. Cockshott, Mr. J P. Holland, Mr. P. G. Morrissey, Mr. P. J. Simons
Zeneca Pharmaceuticals (formerly Imperial Chemical Industries, PLC)
Mereside
Alderley Park
Macclesfield
Cheshire SK10 4TG, England

Dr. Michiko Aoki (Project Leader)
Dr. Kiyoshi Imai (Study Director)
Food and Drug Safety Center
Hatano Research Institute
729-5 Ochiai
Hatano

Kanagawa 25, Japan

The acute toxicity study was conducted for ICI Pharmaceuticals Manufacturing Ltd. by the Food and Drug Safety Center at Hatano Research Institute in Japan. The study was conducted in compliance with Japanese GLP Standards for Safety Studies on Drugs. Study dates ranged from arrival date October 16, to dosing dates November 26 and December 3, 1990.

Preliminary findings:

To determine test groups for this study, two dogs were given propofol. 10 mg/kg was given to one male at 0.5 mg/sec. The dog was anesthetized and recovered after 30 minutes. A second male was given 20 mg/kg. After 14 minutes of anesthesia, the dog died.

Acute Toxicity Study Design:

Dose Groups:

Four beagle dogs (2 male, 2 female/9-10 months) were chosen for each of the following 3 groups:

20 mg/kg (2 mL/kg) = 3X

30 mg/kg (3 mL/kg) = 4.5X

40 mg/kg (4 mL/kg) = 6X

A single injection of propofol was administered into the cephalic vein at 0.5 mg/sec. The dogs were observed for 14 days following the injection. Gross necropsy only was done immediately on any animal that died.

Results:

The dogs in the 20 mg/kg group were dosed first; when none died, four more dogs were given 40 mg/kg. When all four of those dogs died within one minute after the end of propofol administration, the 30 mg/kg group was added to the study. One female at 30 mg/kg died shortly after dosing. All other animals were anesthetized; recovery occurred within 45-60 minutes (30 mg/kg dose) or 20-30 minutes (20 mg/kg dose) after dosing. Over the following 14 days, no adverse effects were noted in the surviving dogs.

The following table provides clinical signs recorded for each dog during the study, including the times during anesthesia when the signs were observed. Times are shown as minutes after starting administration of propofol (given at 0.05 mL/sec):

Dog	Dose mg/kg	Cyanosis	Mydriasis	Cessation Respiration	Cardiac Arrest/	Complete Recovery DEATH
1	20	8-12 min	8-10	-	-	60
2	20	-	-	-	-	60
7	20	-	-	-	-	50
8	20	-	-	-	-	50
5	30	7-15	-	-	-	50
6	30	6-10	9-10	9-10	10	-
11	30	-	-	-	-	50
12	30	15-16	-	-	-	60
3	40	4-14	7-14	12-14	14	-
4	40	11-12	11-12	12	12	-
9	40	14-16	14-16	15-16	16	-
10	40	12-16	15-16	15-16	16	-

The table shows the progression of clinical signs associated with propofol overdose when dogs are spontaneously breathing room air. These signs are not unique to this anesthetic. Cyanosis and mydriasis are relatively early signs of excessive anesthesia that serve as an indication that supplemental oxygen is necessary.

Gross necropsy findings were not specifically pathological for propofol:

- cyanotic oral mucous membranes (all dead dogs)
- hepatic congestion (all 40 mg/kg animals)
- renal cortical congestion (3 dogs in the 40 mg/kg group)
- pulmonary effusion (1 dog in the 40 mg/kg group)
- congestion in lung and GI tract (1 dog in the 30 mg/kg group)
- splenic congestion (1 dog: 30 mg/kg/ 3 dogs: 40 mg/kg)

Conclusion:

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The administration of propofol without respiratory support (oxygen supplementation, ventilation) may be lethal or result in severe respiratory depression at doses equivalent to 3X or greater (>20 mg/kg) than the recommended induction dose.

B. THIRTY DAY IV TOXICITY STUDY IN DOGS:

Study Directors:

Dr. I. D. Cockshott, Mr. J P. Holland, Mr. P. G. Morrissey, Mr. P. J. Simons
Zeneca Pharmaceuticals (formerly Imperial Chemical Industries, PLC)
Mereside
Alderley Park
Macclesfield
Cheshire SK10 4TG, England

The objective of the study was to determine the toxicity of repeated intravenous doses of propofol in the dog over a 30 day period. The study was conducted in the United Kingdom in 1982 using GLP's.

Test Groups:

Ten dogs (5 female and 5 male) were used in each of the following groups:

- Group I = saline control (1 mL/kg)
- Group II = vehicle control (1 mL/kg)
- Group III = 5 mg/kg (0.76X) propofol bolus (0.5 mL/kg)
- Group IV = 10 mg/kg (1.5X) propofol bolus (1.0 mL/kg)
- Group V = 30 mg/kg/day (total of 4.5 X)

Groups I through IV were dosed daily for 30 days before feeding.

For Group V dogs, the entire dose of 30 mg/kg was drawn into a syringe. After the induction dose was given (7.5 mg/kg) the remainder of the dose was infused at a rate of 0.05 mL/kg/minute using an injection pump. The animals in Group V were dosed three times per week during the four week study (total of 13 times).

Prior to inclusion in the study, selected dogs had all given acceptable results in a complete physical examination, including hematology and serum chemistry.

Final selection and allocation to dose groups took place at least 25 days before the first dose. The study was staggered on a replicate basis. Necropsy took place on day 31 of the study.

Test Article:

Propofol (10 mg/mL) was administered to Groups I-IV with a sterile syringe and a 20 gauge, 1 inch needle. The left and right cephalic veins were used on alternate days. Group V dogs were dosed with a

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sterile syringe and a butterfly needle connected to an infusion pump. The injection was given in the left or right saphenous vein.

Rate of Administration:

The intended injection times for Groups I, II, and III were 30 seconds. Group IV injection time was changed from 90 seconds to 60 seconds to avoid problems associated with slower induction such as struggling. The injection times were recorded only if greater or less than 5 seconds of the intended time.

Group V received the induction dose over 60 seconds, and the subsequent infusion over 45 minutes (range 40-55 minutes).

Observations and Measurements:

Physical Examination:

Each dog was given a full veterinary examination at least once prior to the study and during weeks 2 and 4 during the study. Dogs were also assessed twice daily and any abnormalities were recorded.

Daily observations and veterinary examination did not demonstrate any effects due to propofol administration. No dogs became ill or died during the study.

Body Weight:

Individual body weights were recorded twice weekly for two weeks prior to the study and throughout the study. Body weight and body weight gain were unaffected by the administration of propofol.

Food Consumption:

Every day each dog was offered 400 gm of the laboratory diet at approximately the same time. Any remaining food was removed the following morning, the weight was estimated and recorded as a percentage of the amount that was offered. The records begin two weeks before the study until the study ended.

The food consumption of some dogs from all groups, including controls, was lower than normal at times, especially during the second half of the study. Effects on food consumption were not specifically attributable to propofol.

Recovery Time:

The time from the end of dose administration to recovery of consciousness was recorded:

- a. twice during the first week of dosing
- b. once during the second week of dosing

- c. once during the third week of dosing
- d. twice during the fourth week of dosing

The following table represents the group mean values for recovery times in minutes:

	Group III	Group IV	Group V
First dose	5.70	11.20	9.80
Last dose	8.40	25.56	18.15
Difference	2.70	14.24	8.35

The recovery times were dose-related for the daily injection groups (III and IV). The infusion group (30 mg/kg/day) did not remain anesthetized as long as the 10 mg/kg dose group (IV).

As the study progressed, the recovery times lengthened for dogs from Groups III, IV, and V. This increase was statistically significant for Groups IV and V ($p < 0.01$).

A concurrent pharmacokinetic drug withdrawal test was conducted with separate groups of dogs (Cockshott, 1983). Drug withdrawal animals (3 males and 3 females) were added to Groups I, II, and V, and were treated the same as the main test dogs throughout the 30 day dosing period. These dogs were not necropsied, and remained under observation for another 6 weeks. The area under the propofol blood concentration curve for Groups III and IV was not statistically different between the first dose and the last dose. This indicates that propofol did not accumulate with daily administration over 30 days at the same doses that were used in the safety study. Therefore, the increase in recovery times seen with repeated doses is probably not due to drug accumulation.

Physiological parameters:

Physiological parameters were measured on all dogs in Groups I, IV, and V once prior to the study, once during week 2 and once during week 4. The occurrence of apnea was not recorded. The following measurements were made predose and approximately 3 hours after the dose:

- HR, RR, Tdeg.
- ECG

- Direct arterial blood pressure (BP)

No physiological differences between the control groups and the dosed groups were considered to be toxicologically important or related to the administration of propofol.

Hematology and Serum Chemistry:

Blood was collected before dosing from the jugular veins of all animals at the following times:

- a. twice before the study
- b. once during week 2
- c. once during week 4

Hematology included the following:

PCV	Total WBC count
Hb	Differential WBC count
RBC count	Platelet count
Mean RBC volume	
Mean RBC Hb	Prothrombin time
Mean RBC Hb conc.	Partial thromboplastin time
RBC metHb (4 wk only)	

None of the differences between controls and any dosed group mean results were considered of toxicological importance.

The group mean PTT was significantly lower in Group III dogs during the second week of dosing. It was not considered to be of toxicological importance.

Serum Chemistry included the following:

glucose	AST
total protein	ALT
albumin	AP
total bilirubin	CK
BUN	

No serum chemistry changes were considered to be of toxicological importance.

Urinalysis (UA):

Urine was collected by catheterization for cytology and analysis from all animals in Groups I and IV at the following times:

- a. once prestudy
- b. once prior to first dosing
- c. once during week 2
- d. once during week 4

Measurements included the following:

volume	protein
cytology	blood
bilirubin	pH
ketones	specific gravity
glucose	color

None of the changes in the urinary parameters were considered to be of toxicological importance.

Pathology:

Dogs were humanely killed on the day following the final dose. A complete necropsy was done on all dogs and satisfactory tissue samples were collected for histopathology.

Organ weights were taken on adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, pituitary, testes, and thyroid glands.

At necropsy, there were no changes in organ weights or any macroscopic or microscopic tissue changes that were attributed to propofol.

This study supports the safe use of propofol for induction of anesthesia in dogs.

C. INTRAVENOUS INJECTION SITE STUDY:

Study Directors:

Dr. I. D. Cockshott, Mr. J P. Holland, Mr. P. G. Morrissey, Mr. P. J. Simons
Zeneca Pharmaceuticals (formerly Imperial Chemical Industries, PLC)
Mereside
Alderley Park
Macclesfield
Cheshire SK10 4TG, England

Objective:

The study was designed to examine the tolerance of the cephalic vein wall to the intravenous injection of propofol. The study was conducted under GLPs (study dates November 16-18, 1982). Propofol (10 mg/mL) was formulated and tested to the same specifications as the sales formulation.

Test Animals:

Two male and two female beagles (11-16 months old; 12.9-16.4 kg) were acclimated for a week in satisfactory housing.

Study Design:

Each dog received an injection of a control product (sterile saline) into the right cephalic vein and an injection of propofol into the left cephalic vein on three consecutive days. The dose was 10 mg/kg (1.5X). The dose volume for the control and test article was 1 mL/kg, administered at the rate of approximately 1.2 mL/sec (approx. 15 sec). Injections were made using a 25mm X 20 gauge needle. The study did not evaluate pain on injection.

Injection areas were examined immediately before and after injection, approximately 1, 2, and 6 hours after injection on days 1 and 2, and 1 and 2 hours after injection on day 3.

Following humane euthanasia on day 3, approximately 8 cm of cephalic vein was removed from each leg and the following specimens were removed:

- Site A: 1.5 cm, centered 3 cm proximal to the injection site (direction of blood flow).
- Site B: 1.5 cm, centered 6 cm proximal to the injection site.

All these specimens were examined histopathologically, except for the right cephalic (control) of one dog (#37102).

Results:

In two dogs, small volumes of propofol, and in one animal the saline control, were injected subcutaneously on day one. A second, more proximal injection site was used in these dogs. No other abnormal observations were noted.

Necropsy:

Gross: Hemorrhage or blood clot was seen at all injection sites as a result of repeated venipuncture. This was not associated with the administration of propofol since hemorrhage was noted in both legs (control and propofol).

Histopathology: No abnormalities were seen in the walls of the veins examined.

The study satisfactorily examines the potential for tissue irritation at the injection site. Propofol did not produce local irritation when injected into the cephalic vein.

II. THE SAFETY OF RAPINOVET IN CATS WAS INVESTIGATED IN THREE STUDIES:

- A. ACUTE TOXICITY STUDY OF PROPOFOL IN CATS
- B. SAFETY STUDY OF PROPOFOL IN CATS
- C. CLINICAL TRIAL UNDER FIELD CONDITIONS WITH PROPOFOL IN CATS

A. ACUTE TOXICITY STUDY

The objective of this study was to determine the acute toxicity of propofol in cats. The study was conducted by:

Study Director:
Dr. Brian E. Johnson
Liberty Research
P. O. Box 107, Route 17C
Waverly, NY 14892-0107

Sponsor Monitor:
Dr. Donald G. Campbell
Mallinckrodt Veterinary, Inc.
421 East Hawley Street
Mundelein, IL 60060

The study was conducted according to Good Laboratory Practice (GLP) regulations (21 CFR, part 58).

Johnson and Campbell (1997a) conducted an acute toxicity study in cats. Two groups of 4 cats (2 M and 2 F) were given single intravenous doses of propofol at either 19.8 (1.5 times the high end of the induction dose range) or 26.4 (2 times the high end of the induction dose range) mg/kg. Animals were intubated and allowed to breathe room air. If apnea occurred and lasted for longer than one minute, positive pressure ventilation with 100 % oxygen was utilized until spontaneous breathing resumed, at which time room air was supplied through the tube. Observations included: adverse reactions; body weights; clinical signs; serum chemistry; hematology; duration of anesthesia; recovery time; pulse rate; respiratory rate; non-invasive systolic, diastolic and mean arterial blood pressures; hemoglobin oxygen saturation by pulse oximeter; electrocardiogram; gross necropsy and histopathology (26.4 mg/kg group only).

There were no signs of apnea in cats administered 19.8 mg/kg of propofol. Two cats at 26.4 mg/kg experienced apnea lasting longer than one minute. One was resuscitated by positive pressure ventilation with 100 % oxygen, resuming respiration within 5 minutes. The other did not respond to resuscitation and died 13 minutes after induction.

There were no unusual changes in body weights, clinical signs, serum chemistry or hematology values in surviving cats subsequent to propofol anesthesia.

The duration of anesthesia (induction to extubation) was approximately 44 minutes (range 29 - 53 minutes) for the four cats at 19.8 mg/kg. For the three surviving cats at 26.4 mg/kg, the duration of anesthesia was 56 minutes (range 36 - 91 minutes).

Mean recovery time (extubation to standing) was 14.5 minutes (range 12 - 18) for the cats dosed with 19.8 mg/kg. The mean recovery time increased to nearly 39 minutes (range 20 - 62) for the three cats dosed at 26.4 mg/kg.

Pulse rates were not obtained prior to induction of anesthesia. During anesthesia, pulse rates (N = 7) decreased from a mean of 186 beats / minute immediately after induction (range 155 - 226) to a low value of 144 beats / minute (range 138 - 151) at various times after induction. Pulse rates at the last reading prior to extubation averaged 164 beats / minute (range 138 - 186). The animal which died had an initial pulse rate of 211 beats / minute, which decreased to 80 beats / minute at 5 minutes and 0 beats / minute at 10 minutes post-induction.

Respiration rates were not obtained prior to induction of anesthesia. At 19.8 mg/kg, mean respirations were 13.5 breaths / minute immediately after induction (range 6 - 19). The mean low value of 8.5 breaths / minute (range 5 - 12) was reached at various times after induction. Respirations at the last reading prior to extubation averaged 13.0 breaths / minute (range 6 - 19). The animal which died ceased breathing during induction of anesthesia. Cats (N = 3) which received 26.4 mg/kg of propofol (and survived) all recorded the slowest respiration rate immediately after induction, with a mean of 4.7 breaths / minute (range 0 - 12). Respirations at the last reading prior to extubation averaged 26.7 breaths / minute (range 16 - 40).

Blood pressures also were not obtained prior to induction of anesthesia, and values were similar in both treatment groups. Mean systolic, diastolic, and average arterial pressures (N = 7) were 90, 49, and 63 mm Hg respectively at time 0. At 5 minutes, the means (N = 6; one animal not recorded) were 74, 38, and 52 mm Hg, respectively, showing decreases for all three readings. Values during the remainder of anesthesia then generally increased slowly. At the last time point prior to extubation, the mean values (N = 7) were 88, 44, and 58 mm Hg, respectively.

A marked depression of the hemoglobin oxygen saturation was evident immediately following induction (assuming that normal unanesthetized cats would have oxygen saturations above 90 %). Mean values were 65.5 % (range 57 - 74 %) for the cats receiving 19.8 mg/kg, and 23 % (range 20 - 27 %) for those dosed with 26.4 mg/kg. For the cats dosed at 19.8 mg/kg, values increased during anesthesia, with readings consistently above 90 % by 5, 15, 25, and 30 minutes post-induction, respectively. The two non-apnea cats at 26.4 mg/kg were consistently above 90 % by 30 or 45 minutes post-induction, while the cat which received oxygen supplementation early in anesthesia (then returned to room air) was also above 90 % at 45 minutes. The cat which died had a reading of 24 % immediately after induction.

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There were no conduction abnormalities in the electrocardiogram recordings from any of the surviving cats. The cat which died had electrocardiogram tracings which were consistent with cardiac arrest brought on by hypoxia.

Necropsy of the four cats given the 26.4 mg/kg dose (the 3 surviving cats were euthanized 7 days post-treatment) revealed no gross or histopathological changes due to propofol administration.

Doses of propofol above the recommended level will result in longer anesthesia and recovery times. There is a chance of apnea, cardiac arrest, and death immediately after rapid administration of an elevated dose (26.4 mg/kg) of propofol. If apnea occurs, measures such as supplemental oxygen and positive pressure ventilation should be started immediately. Animals which survive this transient (< 5 minutes) crisis show no adverse effects of elevated doses of propofol. Recovery of all cats at 19.8 mg/kg (1.5X the maximum recommended induction dose), without any incidence of apnea, supports the safe use of propofol in cats.

B. MARGIN OF SAFETY STUDY:

The objective of this study was to determine the safety of propofol in cats. The study was conducted by:

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The study was conducted according to Good Laboratory Practice (GLP) regulations (21 CFR, part 58).

Johnson and Campbell (1997b) conducted a safety study in cats. Young adult (less than 1 year of age) domestic shorthair cats were used for this study. Males ranged in weight from 2.79 to 5.09 kg on Day -7, while females were between 2.36 and 3.29 kg. Animals were treated on Days 0, 1, 2, 7, 8, and 9 of the study. Blood samples were collected on Days -7, 0, 2, 7, 9, 16, and 23. On treatment days, the sampling was done after the induction dose of propofol (or the vehicle) was given. Statistical analyses were performed using an average of the Day -7 and Day 0 values as a covariate.

Treatment groups (4 M and 4 F per group) were designated as follows:

Group A (VC)	Vehicle Controls
Group B (IO)	Propofol - 1 induction dose only
Group C (I+3M)	Propofol - 1 induction dose plus 3 maintenance doses
Group D (I+6M)	Propofol - 1 induction dose plus 6 maintenance doses

Group A cats received propofol vehicle (equivalent to a propofol dose of 13.2 mg/kg) in 60 seconds. Animals induced with propofol (Groups B, C, D; 13.2 mg/kg of propofol in 60 seconds) were intubated and allowed to breathe room air. If apnea occurred and lasted for longer than one minute, positive pressure ventilation with 100 % oxygen was utilized until spontaneous breathing resumed. One group received no further treatment (Group B). The second group received three maintenance doses of propofol (4.4 mg/kg), with one dose given each time they started to revive from anesthesia (Group C). The third group received six maintenance doses of propofol in the same fashion (Group D).

The study was conducted in four phases (Phase I, II, III, IV), with one male and one female from each dose group in each phase. Observations included: body weights and food consumption; duration of anesthesia; recovery time; pulse rate; respiratory rate; non-invasive systolic, diastolic and mean arterial blood pressures; hemoglobin oxygen saturation by pulse oximeter; electrocardiogram; hematology; serum chemistry; urinalysis; adverse reactions (clinical signs); gross necropsy (all cats) and histopathology (Groups A and D only).

Body Weight and Food Consumption

Most of the cats (25 of 32) gained a small amount of weight between Day -7 and Day 21. There were no indications of an effect of propofol on body weight.

Food consumption was lower in all cats for the 24 hour periods prior to each treatment, since an overnight fast was required by the protocol. The animals were also fasted prior to blood sampling on non-treatment days. There were no effects of propofol anesthesia on food consumption.

Duration of Anesthesia

Cats in Group A (VC) were not anesthetized. Duration of anesthesia for cats given propofol (Groups B, C, D) was recorded from the end of the induction dose administration to extubation.

Cats in Group B (IO) were anesthetized for a mean of 18.8 minutes (range 13 - 33) on Day 0. Anesthesia time increased slightly on Days 1 and 2, to 20.8 (10 - 31) and 22.0 (14 - 33) minutes. A similar pattern was noted on Days 7, 8, and 9, when the durations of anesthesia were 24.1 (15 - 46), 29.0 (15 - 41), and 34.0 (22 - 43) minutes. The mean duration of anesthesia for this group for the entire study was 24.7 minutes.

The cats in Group C (I+3M) were anesthetized for a mean of 81.1 minutes (51 - 113) on Day 0. Anesthesia time increased on Day 1 to 108.5 minutes (59 - 161). Mean durations were then similar for the rest of the study: Day 2 = 103.6 (71 - 146), Day 7 = 107.1 (75 - 145), Day 8 = 117.6 (87 - 138), and Day 9 = 113.9 (65 - 159). The average for this group for the entire study was 105.3 minutes.

Cats in Group D (I+6M) were anesthetized for a mean of 142.8 (90 - 222) minutes on Day 0. Anesthesia time increased on Days 1 and 2 to 165.3 (115 - 247) and 179.1 (110 - 282) minutes. Mean durations in minutes were 150.5 (106 - 217) on Day 7, 188.1 (144 - 273) on Day 8, and 192.0 (126 - 304) on Day 9. The whole study average was 169.6 minutes of anesthesia in this group.

Physiologic Responses During Anesthesia

Cats in Group A (VC) were not anesthetized, and thus could not be monitored for physiologic responses. Based upon expected normal values for conscious non-premedicated cats (Campbell, 1995; Sawyer and Salsbury, 1995a, 1995b; Peterson, 1997), propofol anesthesia decreased respiration rates, had little effect on pulse rates, decreased blood pressures, and decreased oxygen hemoglobin saturation.

There were no statistically different responses among the propofol treatment groups over time ($P > 0.10$). There were also no differences between the treatment groups for oxygen hemoglobin saturation, blood pressure (systolic, diastolic, and mean), pulse rate, or respiratory rate. Values for these parameters were within normal ranges for non-premedicated cats anesthetized with propofol (Campbell, 1995; Sawyer and Salsbury, 1995a, 1995b; Peterson, 1997).

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Electrocardiogram readings were normal on all but two occasions. One Group C (I+3M) male became apneic on Day 2 with resulting hypoxic arrhythmia. This was resolved following oxygen supplementation. One Group D (I+6M) male had sporadic tall QRS complexes on Day 2. Recovery from anesthesia was uneventful in this cat, and readings were normal at subsequent treatments.

Recovery

Cats in Group A (VC) were not anesthetized, and thus were not monitored for recovery. Duration of recovery for cats given propofol (Groups B, C, D) was measured from extubation to standing.

Cats in Group B (IO) took a mean of 19.3 (8 - 35) minutes to go from the end of anesthesia to standing on Day 0. On Days 1, 2, 7, 8, and 9 the mean recovery times were 27.1 (19 - 35), 26.3 (14 - 37), 24.3 (8 - 42), 28.1 (13 - 42), and 20.5 (5 - 35) minutes. Even though there were some increases during the study, the similarity between recovery times on Day 0 and Day 9 suggests that multiple days of single doses of propofol did not affect this parameter. The overall mean recovery time for Group B (IO) for the entire study was 24.7 minutes.

The cats in Group C (I+3M) required a mean of 23.3 (9 - 51) minutes for standing recovery on Day 0. On Days 1, 2, 7, 8, and 9 the mean recovery times were 27.8 (14 - 50), 30.4 (8 - 58), 24.8 (11 - 45), 34.0 (4 - 67), and 35.3 (9 - 68) minutes. Overall recovery time for Group C (I+3M) for the entire study was 29.2 minutes, a five minute increase over Group B (IO). This was due primarily to the increased times on Days 8 and 9, indicating a slight effect of multiple days dosing at this level on recovery from propofol anesthesia.

Cats in Group D (I+6M) were observed with a mean of 29.3 (16 - 39) minutes for standing recovery on Day 0. Substantially longer recovery times were noted on later treatment days. On Days 1, 2, 7, 8, and 9 the mean recovery times were 61.9 (26 - 83), 47.3 (6 - 87), 36.0 (23 - 63), 51.8 (34 - 65), and 57.5 (35 - 100) minutes. Average recovery time for Group D (I+6M) for the entire study was 47.3 minutes, nearly double the mean for Group B (IO) and 18 minutes longer than the mean for Group C (I+3M).

Red Blood Cell Indices

Erythrocyte count - On Days 2, 7, and 9, Group A (VC) cats had higher erythrocyte counts than cats from the treated groups. On Day 16, there were no differences between any of the groups. On Day 23, Group C (I+3M) had a higher erythrocyte count than any of the other groups.

Hemoglobin - On Days 2, 7, and 9, Group A (VC) animals had higher hemoglobin values than cats in the treated groups. On Day 16, there were no differences between any of the groups. By Day 23, the Group C (I+3M) cats had higher hemoglobin values than Group A (VC) or Group B (IO) animals. The hemoglobin value is related to the erythrocyte count and shows a similar trend.

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Hematocrit - On Days 2, 7, and 9, Group A (VC) cats had higher hematocrit than cats in the treated groups. On Day 16, there were no differences between any of the groups. By Day 23, Group C (I+3M) cats had higher hematocrit values than the other three groups. Hematocrit is related to the erythrocyte count; therefore, the same findings were reflected in the numbers of erythrocytes.

Mean corpuscular volume and mean corpuscular hemoglobin - On Day 7, both MCV and MCH were higher in Group D (I+6M) than in Group A (VC). The clinical significance of this isolated finding is unknown.

Mean corpuscular hemoglobin concentration - A significant group effect ($p < 0.05$) was observed for MCHC. Animals in Group D (I+6M) had higher MCHC values than the other groups throughout the study.

Heinz Bodies

By Day 2, Group D (I+6M) cats had a higher number of Heinz bodies than Group A (VC). On Day 7, all of the treated groups had a significantly higher count of Heinz bodies than the control group. All treated groups showed an increase in Heinz bodies over the dosing period, and all had Day 23 values that were increased over the pretest values. In 10 of 24 treated cats the Heinz bodies remained above 10% on Day 23. There were no indications of anemia in treated cats (see RBC hemoglobin, above, and plasma hemoglobin, below), indicating that treated animals tolerated the increase in Heinz bodies under these study conditions.

White Blood Cell Indices

While there were statistically significant differences in total leukocyte counts among the groups, the differences did not indicate a dose-response relationship with propofol. Higher lymphocyte counts in the control cats were most likely a physiological response (lymphocytosis) to the restraint required for sample collection. Higher monocyte counts were noted in group D (I +6M) compared to Group A (VC) on day 23. Whether the increase in monocytes was due to two cats in Group D that received thermal burns during the study (see clinical signs, below) remains inconclusive.

Platelets

On Day 16, Group C (I+3M) had a significantly lower platelet count than Group B (IO) and Group D (I+6M); however, this value was not different from that of Group A (VC). One animal in Group C had platelet counts throughout the study period that were consistently lower than the other animals in the study, which may have caused some bias in the test. All platelet counts were extremely variable from sample-to-sample and from cat-to-cat. There does not appear to be any relationship between this finding and administration of propofol.

Serum Chemistry

There were no statistically significant differences for sodium, chloride, aspartate amino transferase (AST), alanine amino transferase (ALT), blood urea nitrogen (BUN), or creatinine. Glucose values were nearly identical at all time points and were not analyzed.

Although statistically significant differences among the treatment groups were seen, the pattern was not indicative of a dose-response relationship for the following variables: phosphorus, albumin, bile acids and triglycerides. Bile acids and triglycerides were always higher on treatment days, probably due to the lipid nature of the vehicle. Transient decreases that were no longer apparent by Day 23 occurred in calcium, potassium and alkaline phosphatase.

Globulin - On Day 2, cats from the treated groups had lower globulin values than Group A (VC) cats. No differences were observed on Days 7 or 9. By Day 16, Groups C (I+3M) and D (I+6M) had higher globulin values than Group A (VC).

Total Protein - There were no group differences on Day 7. On Days 2 and 9, the control group had a higher total protein value than any of the treated groups. On Day 16, Group A (VC) had lower total protein values than Groups C (I+3M) and D (I+6M). On Day 23, the Group A (VC) value was lower than Group C (I+3M).

Plasma Hemoglobin - The control group had higher plasma hemoglobin values than any of the treated groups. This observation was likely an artifact of blood collection and not a direct result of propofol administration. Blood was collected from control animals while they were fully conscious, which increased the difficulty of collection with a concomitant increase in inadvertent hemolysis.

Urinalysis

Some urinalysis parameters were nearly identical on all cats at all time points and were not statistically analyzed (glucose, bilirubin, and urobilinogen). Color and consistency were also not analyzed because of possible differences in collection technique (non-absorbent litter substitutes vs. cystocentesis).

The samples were microscopically examined for the presence of casts, cells, crystals, and bacteria. No statistical analysis was performed on these results, nor were any consistent treatment related differences noted.

There were no statistically significant differences with respect to time or treatment group in terms of specific gravity, pH, creatinine, or protein concentration. Four males had persistent low-levels of ketones present (one Group A, two Group B, one Group D); none of these animals appeared clinically abnormal and the values remained at a constant level or fluctuated without any discernible pattern.

Adverse Reactions (clinical signs)

Two cats in Group D (I+6M), dosed during Phase I, suffered thermal burns on the right lateral abdomen due to insufficient padding on the heating pads. By day 23, healing of the burns was well-advanced. The amount of padding was increased during Phases 2, 3, and 4, and no other animals were affected.

No consistent treatment related clinical signs were noted in cats on study. Occasional signs of lacrimation, soft stools, or diarrhea were observed in cats from both the treated and control groups.

Gross Necropsy and Histopathology

A complete gross necropsy was performed on all cats in this study. Findings included kidney lesions typical of healed infarcts, lip lesions consistent with eosinophilic granuloma complex, splenic enlargement probably due to euthanasia with pentobarbital, and one Group B (IO) cat with several small dark foci on the pancreas. None of the findings appear to be related to propofol administration.

Microscopic examination was performed on tissues from all animals in Group A (VC) and Group D (I+6M). There were no microscopic findings that were considered to be treatment related.

C. CLINICAL FIELD TRIAL:

Side effects and other observations were recorded in the clinical field study conducted by Peterson (1997). The design and details of the study were described in the efficacy section above. For each observation listed below, the total number of cases (N) is also presented.

One cat went into cardiac arrest during early recovery, but was successfully resuscitated. The cat was administered butorphanol as a premedication, propofol for induction (10.1 mg/kg over 70 seconds), and was anesthetized sufficiently to complete the procedure (castration). Either butorphanol or propofol separately, the combination of the two, or increased susceptibility of the patient to cardiac arrhythmia may have been the cause of this adverse reaction.

A second cat was prescribed pancuronium bromide, a paralytic, during an MRI examination. The cat was ventilated with a respirator. This cat did not resume spontaneous respirations until 6 hours post-induction. This was due to ventilation and the use of a paralytic agent, and was not attributable to propofol.

Respiratory side effects during the entire study included: cyanosis (5); apnea (3); and sneezing (1).

Neurological side effects included: excitation (8); opisthotonus (1); nystagmus (1); excessive depression (1); and slight delirium (1).

Musculature side effects were: paddling (24); tenseness (7); fasciculations (5); and twitching (2).

Gastrointestinal side effects were: emesis / retching during the procedure (3).

Cardiovascular side effects included: hypotension (9); tachycardia (1); sinus block (1); and premature ventricular contractions (1).

Other side effects were: chewing and licking at the injection site during early recovery (4); slow recovery (2); intravascular pain (2); and rubbing at the face or nose during recovery (1).

Some of the side effects noted during recoveries from propofol were also noted for recoveries from the inhalants with similar incidence (propofol : inhalant), e.g., paddling (8:16) and apnea (1:2).

The side effects were, overall, transient and resolved on their own. The side effects noted during the field study were not unique to propofol but are also typically observed in any population receiving anesthesia regardless of the anesthetic agent.

6. SUPPORTIVE STUDIES:

DOGS:

a. Sighthounds:

1. Robertson, et al. (1992) determined the cardiopulmonary, anesthetic, and postanesthetic effects of intravenous infusions of propofol in Greyhounds (n = 6) and non-Greyhounds (n = 7). Dogs were premedicated with atropine and acepromazine, anesthesia was induced with propofol (4.0 mg/kg in greyhounds, 3.2 mg/kg in non-greyhounds), then maintained by infusion at 0.4 mg/kg/minute. Recovery was approximately 30 minutes slower in Greyhounds.

2. Zoran, et al. (1993) compared the pharmacokinetics of propofol using 8 mixed-breed dogs and 10 greyhounds. Anesthesia was induced with 5 mg/kg of propofol, with additional drug given if needed for intubation. Disposition of propofol was adequately described by a two-compartment model. Greyhounds had higher propofol levels in plasma, a lower volume of distribution, slower total body clearance rates, and longer recovery times than did mixed-breed dogs. The elimination half-life was similar in both groups. This report confirmed that recovery may be slower in greyhounds, and provided an explanation based upon differences in pharmacokinetics.

3. Mandsager, et al. (1993) determined the effects of chloramphenicol on the pharmacokinetics of propofol in greyhound dogs. Thirty minutes prior to anesthesia, two groups of 5 dogs each were given intravenous doses of either saline or chloramphenicol (50 mg/kg). All dogs were induced with 10 mg/kg of propofol and maintained by infusion at 0.4 mg/kg/minute. Chloramphenicol (a cytochrome P-450 inhibitor) increased the half life of propofol by 209 %, decreased body clearance by 45 %, and prolonged recovery by 768 - 946 %. This report shows that other medications may alter the pharmacokinetics of propofol.

b. Arrhythmogenicity:

Kamibayashi, et al. (1991) determined the effects of propofol on epinephrine-induced arrhythmias in dogs. They used 62 dogs anesthetized with propofol (N = 8; 10 mg/kg bolus followed by 40 mg/kg/hr infusion), halothane (N = 8), etomidate (N = 8), etomidate/ alcuronium (N = 8), etomidate/alcuronium plus propofol infusion (5, 10, or 20 mg/kg/hr; N = 8, 7, and 7, respectively), and etomidate plus propofol vehicle (N = 8). Epinephrine was infused at 60 minutes after the start of anesthesia. Propofol enhances epinephrine-induced arrhythmias in a dose-dependent manner, similar to several other anesthetic agents (for example, thiopental and halothane).

c. Propofol Pharmacokinetics:

1. Cockshott (1983) performed HPLC analyses of plasma samples from dogs during the pharmacokinetic drug withdrawal test that was conducted with the main target animal safety study (Morrisey, 1983). The pharmacokinetics fitted a two compartment open model. Following bolus doses of 5 or 10 mg/kg, propofol was rapidly distributed into a large apparent volume of distribution (81 L). Propofol clearance was characterized by an elimination half-life of 27 minutes. After an induction dose followed by maintenance infusion, steady state propofol plasma concentrations were achieved within 25 minutes of the start of the infusion. The mean concentration at steady state was 6.2 g/mL. The elimination half life was 35 minutes.

2. Cockshott et al. (1992) published a second study which also involved single doses or induction doses followed by infusion. In the first part of the study, 3 dogs were given 7 mg/kg of propofol. Two weeks later, they were dosed with 7 mg/kg followed by infusion at 0.47 mg/kg/min for 6 hours. In the second part of the study, 8 male and 8 female dogs were induced with 7.5 mg/kg followed by infusion of 0.5 mg/kg/min for 4 hours, four times within 2 weeks. The pharmacokinetics of propofol were best described by a three compartment model. Following a single injection, there was a large initial volume of distribution (1.4 L/kg), and extensive redistribution (11.4 L/kg). The total body clearance was rapid (76 mL/kg/min). After the infusion dose, the volume of distribution (1.0 L/kg) was similar, but the redistribution compartment was less (6.6 L/kg). The total body clearance rate was slower (34 mL/kg/min).

d. Propofol Metabolism:

1. Simons (1983) administered ¹⁴C propofol to 3 male and 3 female dogs. The dose given was 9.7 mg/kg. The excreta were collected, and plasma samples were collected through 120 hours after dosing. Recovery was approximately 60 % in the urine and 29 % in the feces. Urine metabolites included glucuronic acid (24

%) and sulfate (22 %) conjugates of 2,6 di-isopropyl 1,4 quinone. The feces contained 2,6 di-isopropyl 1,4 quinone (4 %) and polar metabolites which were not identified. The apparent elimination half-life of propofol from plasma was approximately 24 minutes.

2. Simons et al. (1991) published the results of a second study which included both induction and induction plus maintenance. Male dogs (N = 3) were given a single propofol dose of 7.2 mg/kg. One month later, they were dosed with 7.3 mg/kg followed by infusion at 0.47 mg/kg/min for 6 hours. Elimination was approximately 70 % in urine and 30 % in feces, and was similar for single doses and infusion administration. Propofol metabolism shifted during the 6 hours of infusion, from the sulfate conjugates to more glucuronic acid conjugates.

e. Effects of propofol on pharmacokinetics and metabolism of propranolol:

Perry et al. (1991) determined the effect of propofol on drug distribution and metabolism of propranolol. On the first of two successive days, the procedure was performed in 6 awake dogs. On the second day, anesthesia was induced with 8 mg/kg and maintained with 0.8 mg/kg/minute of propofol. Propofol reduced intrinsic clearance of propranolol by 40 %, increased the volume of distribution, and increased the free-fraction (non-protein bound) of propranolol. These results show that propofol may have effects on the pharmacokinetics or metabolism of other drugs administered to dogs.

CATS:

f. The effects of consecutive day propofol anesthesia on feline red blood cells:

Andress et al. (1995) conducted a study in cats at Mississippi State University. Six healthy cats were administered propofol for induction at 6 mg/kg, then maintained for 30 minutes by propofol infusion (0.2 to 0.3 mg/kg/min). The protocol called for cats to be anesthetized once a day for 10 consecutive days, with predetermined criteria for discontinuing daily infusions if necessary.

Recovery time significantly increased from Day 1 to Day 2. Following the third consecutive day of propofol anesthesia there was a significant increase from baseline in the mean percentage of Heinz bodies. Five of six cats developed generalized malaise, anorexia, and diarrhea on Day 5, 6, or 7, and two cats developed facial edema. The mean number of consecutive days of propofol anesthesia was 6, and no cats were treated more than 7 days. All clinical signs resolved without treatment 24 to 48 hours after discontinuing propofol anesthesia. This study suggests that consecutive day anesthesia in normal cats may result in increased recovery times, may induce oxidative injury to feline red blood cells in the form of excessive Heinz body formation, and may result in clinical signs of illness.

7. HUMAN USER SAFETY:

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of the NADA. This drug is labeled for use in dogs and cats, which are non-food animals.

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Labeling contains adequate warnings against accidental self-administration and the risk of drug diversion. An "800" number is provided by the sponsor for the provision of Material Safety Data Sheets (MSDS).

8. AGENCY CONCLUSIONS:

The data in support of this NADA comply with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and Section 514.111 of the implementing regulations. It demonstrates that Rapinovel (propofol) Anesthetic Injection, when used under labeled conditions of use, is safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is judged to be critical in the administration of a drug that provides induction and maintenance of general anesthesia. If the product is used without the knowledge necessary for understanding the physiological effects of propofol and its potential interactions with other drugs commonly used before and/or during general anesthesia, the efficacy of the drug may change, and the safety of the animal could be jeopardized.

Under Section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act (FFDCA), the original canine approval qualified for FIVE years of marketing exclusivity beginning on the date of approval (November 7, 1996) because no active ingredient (including any ester or salt of the active ingredient) of the drug, had been approved in any other application.

Under Section 512 (c)(2)(F)(iii) of the FFDCA, this feline supplemental approval qualifies for three years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, or any studies of animal safety, required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the cat for which the supplemental application was approved.

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10. LABELING:

- Package Insert
- Ampule Label
- Carton Label